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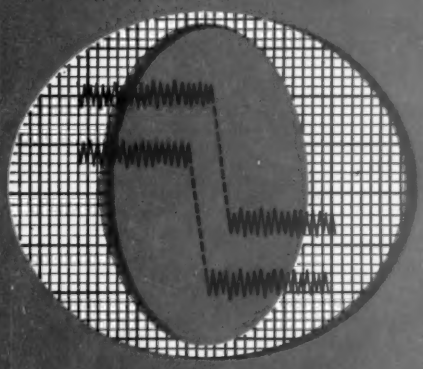

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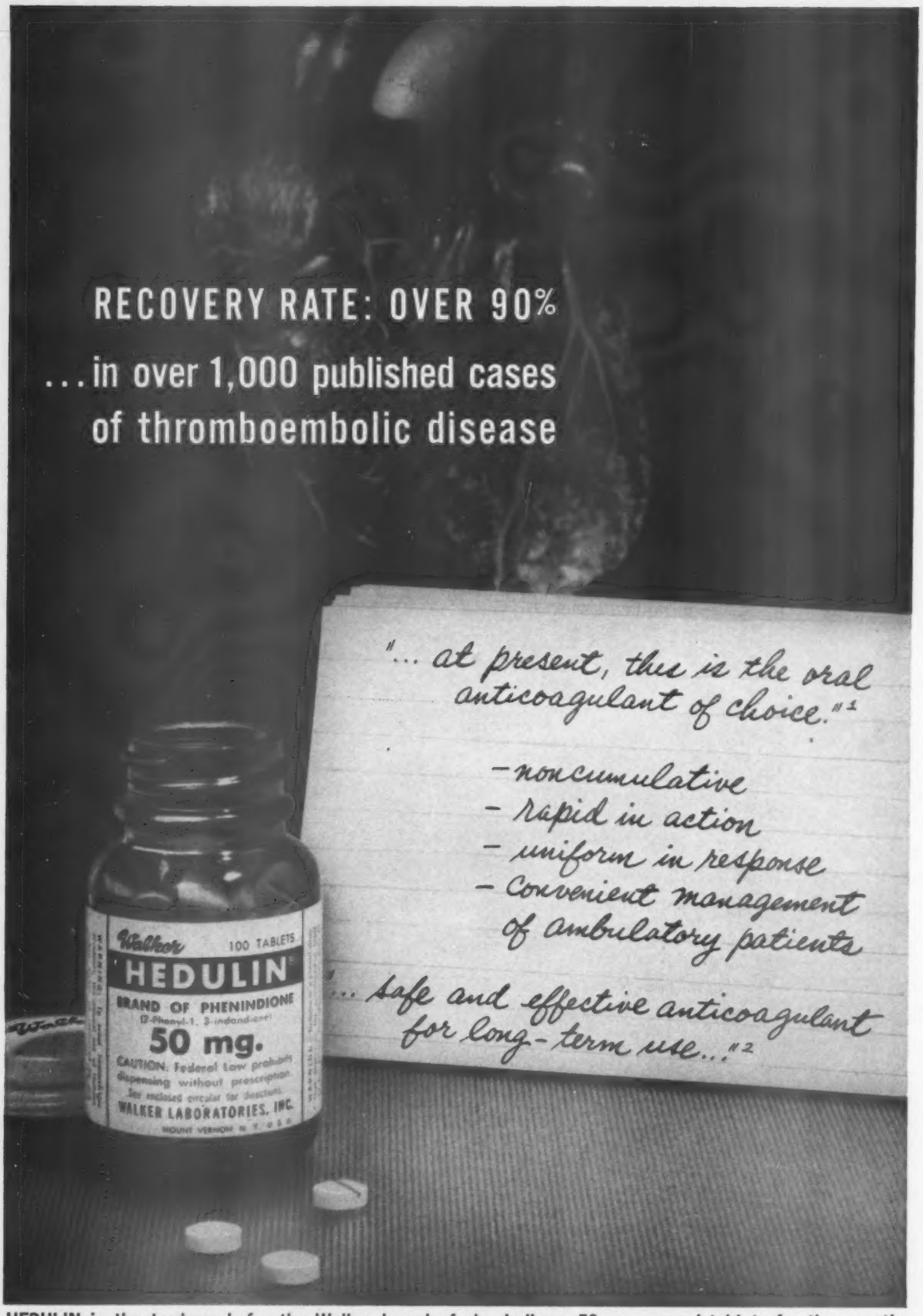
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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

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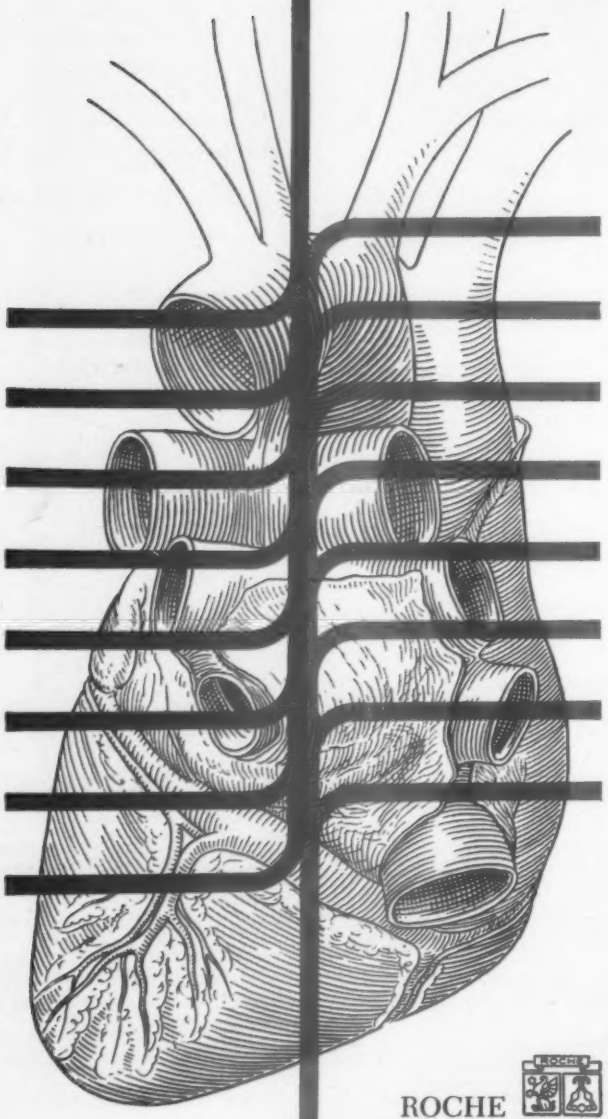

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Volume V MARCH 1960 Number 3

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Clinical Studies

Absorption of I^{131}-Triolein in Congestive Heart Failure
JUHA HAKKILA, TOUKO E. MÄKELÄ AND PENTTI I. HALONEN 295

From Finland comes this study relating deficient absorption of fat to heart failure. Investigating the absorption of I^{131}-triolein into the blood and the fecal excretion of I^{131} activity in seventeen patients with congestive heart failure and twelve control subjects without congestive heart failure or gastrointestinal disease, the authors found that the lipid-bound activity in the blood is clearly decreased and retarded in patients with congestive heart failure. With improvement in the state of heart failure the absorption of fat definitely increases. They present several possible causes for deficient fat absorption in heart failure.

Cardiac Adrenergic Preponderance Due to Lack of Physical Exercise and Its Pathogenic Implications . . . . . W. RAAB, P. DE PAULA E SILVA, H. MARCHET, E. KIMURA AND Y. K. STARCHESKA, WITH THE TECHNICAL ASSISTANCE OF H. DEMING, W. LISSAUER, G. MARCHET AND E. STAUDINGER 300

The influence on the basic cardiac neurovegetative status at rest of habitual vigorous exercise and its lack was studied in 360 healthy American and Austrian men in the Alps of Austria and the Green Mountains of Vermont. A linear increase of cardiac sympathetic tone and a decline of cardiac neurovegetative counterregulatory effectiveness occurred in proportion to decreasing degrees of habitual exercise. Physical training periods reversed the process. Smoking habits left the basic cardiac neurovegetative status unaltered. The hazards of cardiac adrenergic preponderance due to lack of physical exercise are discussed. A practical offshoot of this carefully planned study is the obvious need for the development of medically supervised, prophylactic reconditioning programs for degenerating sedentary populations.

An Index for the Measurement of the Degree of Aortic Incompetence
IAN F. S. MACKAY 321

Under certain conditions a blood pressure cuff may act as a valve on the peripheral blood vessels. A pneumatic cuff was employed as a valve on the brachial artery in aortic incompetence, and by obstructing the regurgitant blood a means for measuring its volume was devised. The essential feature of this technic is the measurement of the forearm-hand blood flows by venous occlusion plethysmography with the limb in the upward and vertical position, at high ambient temperatures of 30° to 32°C. The present method has not as yet proved of much clinical value, but it can demonstrate a high degree of regurgitation.

Factors Affecting the Pulmonary "Capillary" Pressure
BERNARD L. CHARMS, BERNARD L. BROFMAN AND ARNOLD ADICOFF 328

Temporary unilateral pulmonary artery occlusion by a balloon produces the same conditions that are obtained by wedging a cardiac catheter into the pulmonary artery. With this method distal pressures correlated well with pulmonary capillary pressures. In pulmonary emphysema the distal and pulmonary capillary pressures varied greatly with respiration, occasionally reaching considerably elevated levels during expiration. The authors maintain that greater intrapleural pressures generated in the emphysematous patient are most significant in producing a further increase in pulmonary artery pressure rather than implying involvement of the pulmonary vasculature. It seems inadvisable to calculate changes in pulmonary resistance using an assumed or static capillary pressure since an apparently increased pulmonary arterial-pulmonary capillary gradient may not be an actual or effective one, especially in patients with emphysema.

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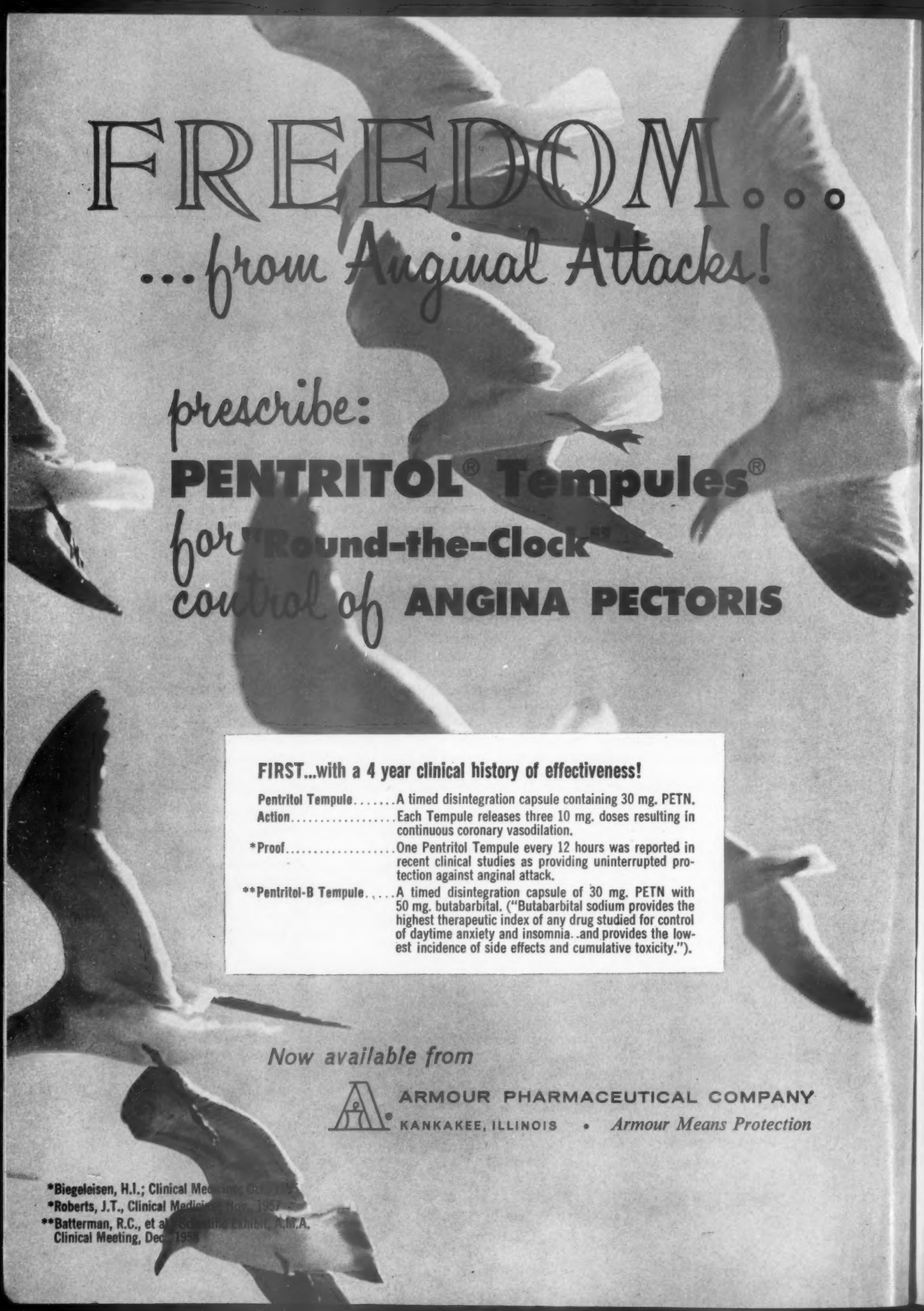

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*Biegeleisen, H.I.; Clinical Meeting, Oct. 1957

*Roberts, J.T., Clinical Medicine, Nov. 1957

**Batterman, R.C., et al, Scientific Exhibit, A.M.A. Clinical Meeting, Dec. 1958

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The "Straight Back" Syndrome. A New Cause of Pseudoheart Disease
MAURICE S. RAWLINGS 333

The "straight back" syndrome is a hitherto unrecognized deformity of the chest causing pseudoheart disease. It represents a congenital loss of the normal, gentle kyphotic curve of the upper dorsal spine and is the opposite of "funnel chest." It produces a decrease in the anteroposterior diameter of the chest, causing false enlargement of the heart in the frontal view, and compresses or kinks the great vessels, causing mechanical systolic murmurs near the base of the heart or over the precordium. The condition is easily recognized when lateral x-ray views of the chest are taken. Recognition of this condition may prevent a common form of iatrogenic heart disease.

The Electrocardiographic Findings in Pulmonary Emphysema . . DAVID LITTMANN 339

Early in pulmonary emphysema the electrocardiogram is normal with ÂQRS and ÂP approximately +90 degrees. As the emphysema progresses, the standard and precordial leads acquire S waves and P becomes larger. Later all standard and unipolar limb leads become equiphasic and ÂQRS becomes indeterminate, assuming a position at right angles to the frontal plane of the body. Precordial leads V_1 through V_5 become negative and ÂQRS is directed backwards. By this time the pattern of peaked P pulmonale has developed with an electrical axis remaining at +90 degrees. Other electrocardiographic manifestations of emphysema include T wave abnormalities of right ventricular strain and the more classic but less common right ventricular hypertrophy and right bundle branch block. A pattern resembling myocardial infarction may also be found. Many of these changes are due to altered conduction pathways or altered extracardiac conductivity of the electrical events of the heart.

The Vectorcardiogram in Chronic Chagas Myocarditis. An Analysis of the Intraventricular Conduction Delays Associated with a Superiorly Oriented ÂQRS
JOZEF FÉHÉR, FÚLVIO PILEGGI, VITOR TEIXEIRA, JOÃO TRANCHESI, FRANCISCO XAVIER PINTO LIMA, OSWALDO SPIRITUS, MORIS CHANSKY AND LUIZ V. DÉCOURT 349

A complete right bundle branch block pattern associated with a superiorly oriented ÂQRS is highly characteristic of the chronic stage of Chagas myocarditis. These findings occurred in ten of fourteen patients and were confirmed by vectorcardiography. In addition, the vectorcardiograms disclosed intraventricular conduction disturbance, probably at the level of the connections of the Purkinje fibers with the myocardium, and loss of electrical forces due to myocardial fibrosis. The remaining four patients showed signs of left ventricular hypertrophy with delay predominantly in the terminal portion of the QRS loop.

Experimental Study

A New Approach for the Recognition of Ventricular Premature Beats
ABDO BISTENI, DEMETRIO SODI-PALLARES, GUSTAVO A. MEDRANO AND FÚLVIO PILEGGI 358

Experimental work on the dog's heart enables these investigators to define a new concept of ventricular extrasystoles. For them ventricular extrasystoles are those that show ventricular complexes with morphologies of advanced degree of block (third degree), when such extrasystoles occur during the electrical diastolic phase between T and P. Those with morphologies showing incomplete bundle branch block (first and second degrees) or normal QRS morphology are also ventricular premature beats when produced in the electrical diastolic phase between P and the beginning of QRS.

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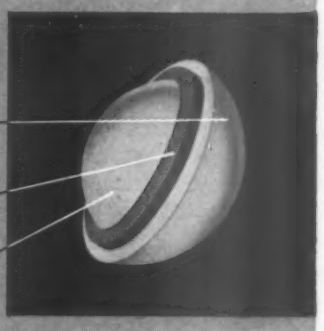

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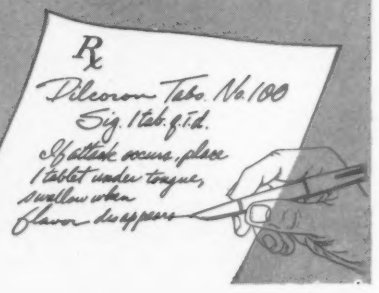

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Reviews

Heart Failure from the Point of View of Quantitative Anatomy. . A. J. LINZBACH 370

The author adduces a refreshingly novel concept of heart hypertrophy and failure with pragmatic and theoretical value. Increases in heart weight above the critical level of 500 gm. are due to increase in the number of fibers with little further thickening. Capillaries also increase with a ratio of one capillary per fiber maintained. The coronary insufficiency associated with advanced hypertrophy is not principally due to a failure of supply but to the fact that the growth of the coronary arteries is retarded and atherosclerotic lesions become more frequent. Structural dilatation of the heart results from coronary insufficiency and forms the morphologic substrate of the decompensated heart. Cardiac insufficiency then results, not from overstretching of the fibers or inadequate oxygen consumption per fiber length but from strictly mechanical reasons. The unit muscle weight may produce a normal amount of energy liberated on contraction but it is no longer adequate to expel a normal stroke volume from a ventricle of these dimensions.

A New Concept of Cardiac Failure . . . . . .BRUNO KISCH 383

Changes in the sarcosomes of failing hearts have been shown by electron microscopy. These findings indicate not only that biochemical changes in intercellular and intracellular locations are responsible for the abnormal cardiac function, but also that a morphologically well recognizable change in the appearance and number of the enzyme-bearing sarcosomes is involved, probably as a causative factor.

New Method

The Vectorelectrocardiogram. A Simple Method of Recording and Interpreting the Spatial Electrical Fields of the Heart
J. LOUIS FREIBRUN, JULIEN H. ISAACS AND GEORGE C. GRIFFITH 390

A simple, inexpensive and practical technic for recording the spatial vector potentials of the heart is described and illustrative vectorelectrocardiograms are presented. The value of this method is that the standard office electrocardiograph machine may be used. The interpretation of the vectorelectrocardiogram is based on timing, spatial orientation and relative magnitudes of the instantaneous vectors. Correlation with known clinical and pathologic data has been excellent.

Reports on Therapy

Hydroflumethiazide. The Clinical Pharmacology of a New Oral Diuretic
EDWARD W. DENNIS AND RALPH V. FORD 402

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The Clinical Pharmacologic Investigation of a New Benzothiadiazine Diuretic, CMR-807 . . . . . RALPH V. FORD 407

A new benzothiadiazine derivative, CMR-807, proves to be a more potent, orally effective diuretic than similar diuretic agents. It produces less potassium and bicarbonate loss with a lessened tendency toward hypokalemic manifestations. It is effective in repeated doses and showed no toxicity in this study.

The Use of Hydroxyzine in the Prophylaxis and Therapy of Cardiac Arrhythmias ALBERT M. ZIFFER AND SOLOMON D. KLOTZ 413

The anticipated antiarrhythmic effect of hydroxyzine on cardiac arrhythmias was not achieved in ten of thirteen subjects carefully tested. While receiving this medication one patient reverted to sinus rhythm while a severe arrhythmia developed in another. The only favorable responses occurred in a sixty-five year old woman with nodal tachycardia and in an eighty-five year old woman with frequent ventricular extrasystoles. Chiefly responsible for the improvement was the ataractic effect of the drug. In two patients with atrial tachycardia the atropine-like effect proved undesirable since the degree of atrioventricular block decreased and the ventricular rate rose.

Maintenance Quinidine Therapy. Value of Enteric-Coated Quinidine Tablets DAVID W. RICHARDSON, MARGARET E. ZEE AND EUGENE M. WYSO 417

Blood levels of quinidine following the administration of delayed absorption quinidine sulfate tablets were compared with those obtained following the administration of quinidine sulfate U.S.P. in a commonly used maintenance dosage schedule. It was demonstrated that long-acting quinidine sulfate administered twice daily, produced relatively constant blood levels within an effective range throughout the day and night whereas greater fluctuation in blood level was obtained with U.S.P. quinidine administered four times daily.

Historical Milestones

Emotions and Angina Pectoris. An Historical Review . . . SAMUEL J. KOWAL 421

Emotions, such as passion, rage, joy and anger, have long been known to induce and precipitate angina pectoris, often with fatal consequences. Despite the results of such emotions on the heart, cardiac patients are either unwilling or unable to avoid them. Physicians are among the worst offenders with a high incidence of angina pectoris. Worry and hard work also appear to be contributing factors. A fundamental question raised by the writer is how a disease with the dramatic qualities of angina pectoris could have remained unnoticed in both medical and non-medical literature over the many centuries during which man recorded his observations of himself and the world.

Special Departments

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References:
1. Summary of Case Reports on File, Ives-Cameron Company (1958-1959). 2. Riseman, J.E.F., et al.: Circulation 17:22 (Jan.) 1958. 3. Russek, H.I.: Personal Communication (Oct., 1959). 4. Case Reports on File, Ives-Cameron Company (1958-1959). 5. Albert, A.: Personal Communication (Oct., 1959). 6. Sherber, D.A.: Personal Communication (Oct., 1959).

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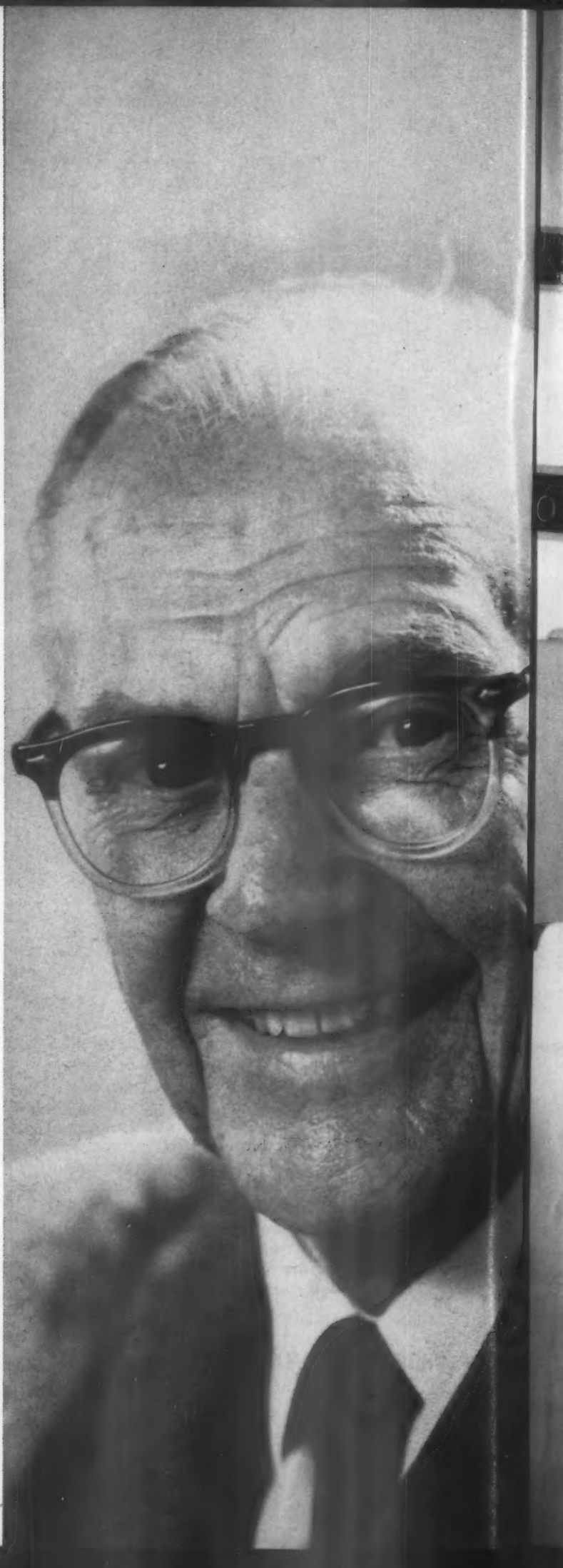

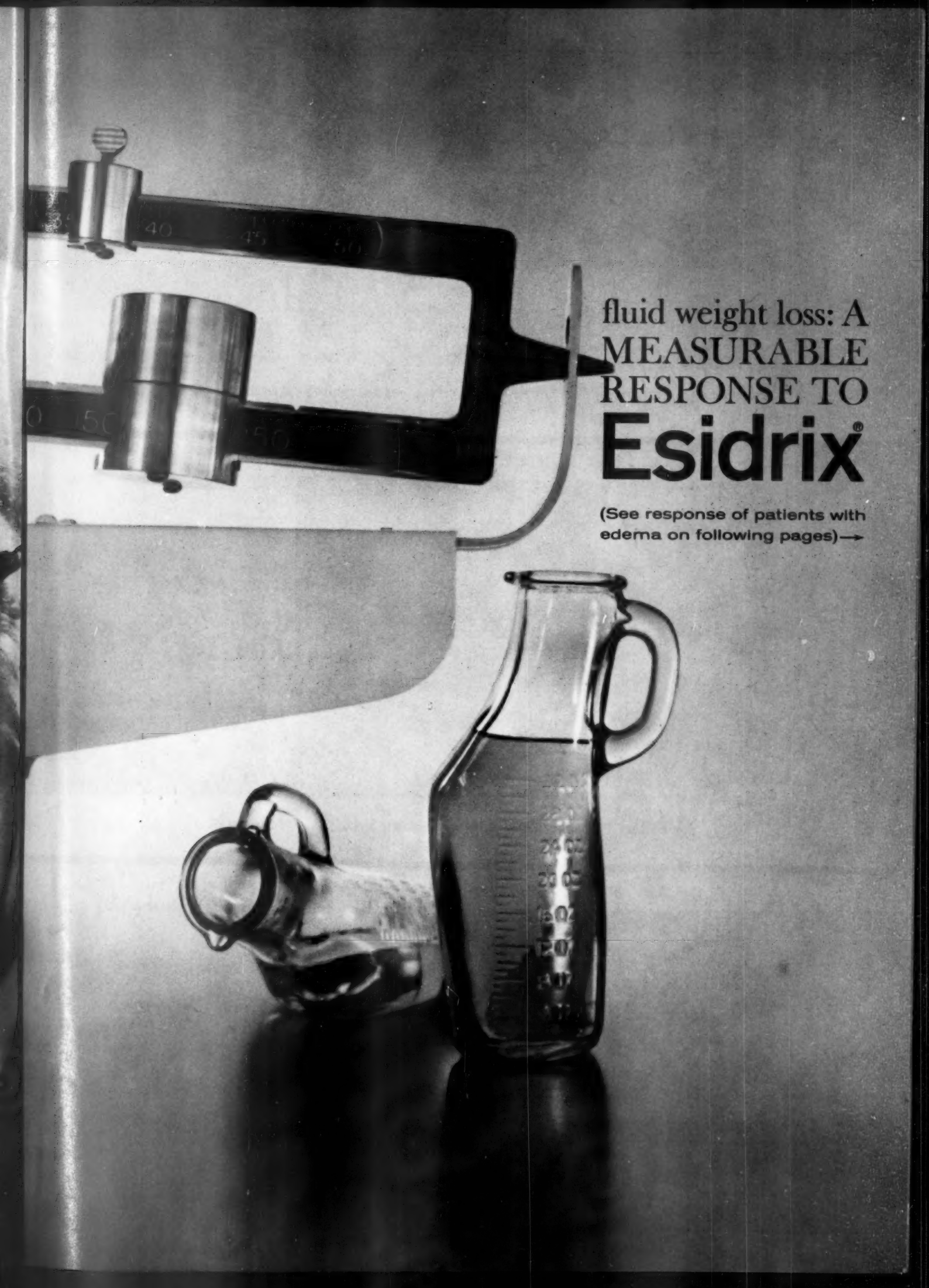

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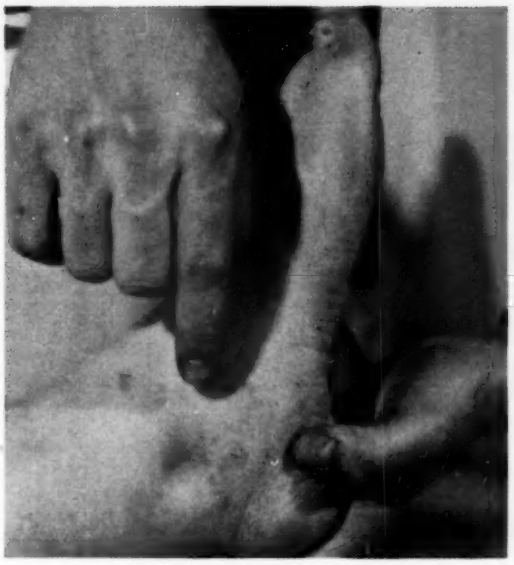

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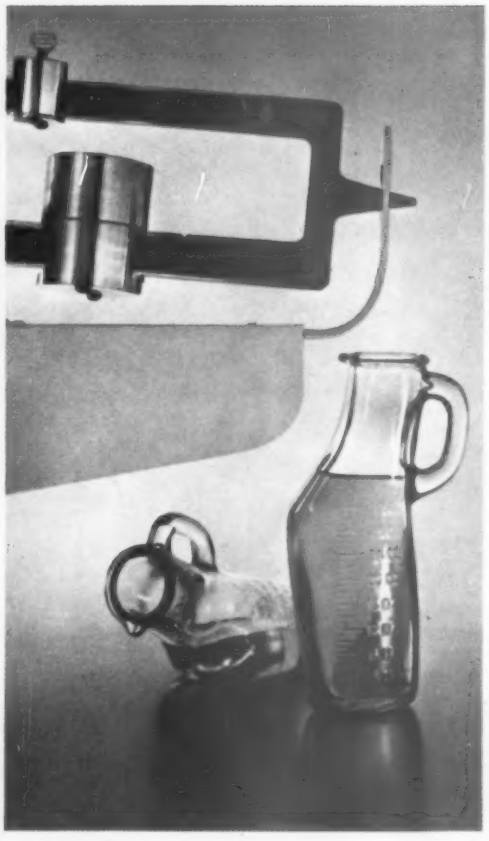

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1. Bellet, S.; Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.
3. Finkelstein, D.: Penn. Med. J. 61:1216, 1958.

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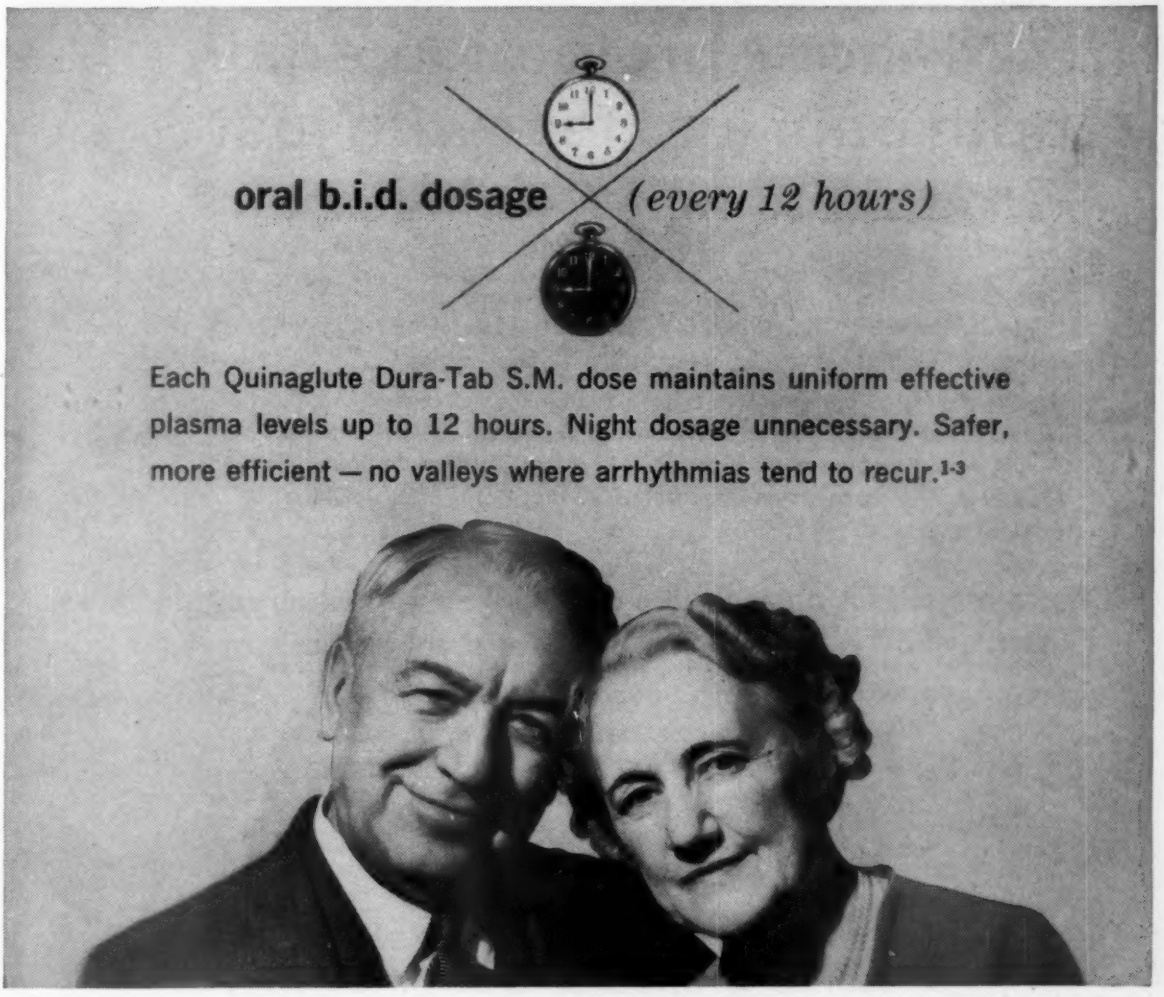
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1. Feinblatt, T. M., and Ferguson, E. A.: New Eng. J. Med. 256:331 (Feb.) 1957.
2. Kupersmith, I. H.: International Record of Medicine, Vol. 171 No. 10 (Oct.) 1958.
3. Berry, J. W., and Roach, T. C.: Circulation, Vol. 17, No. 6 (June) 1958.

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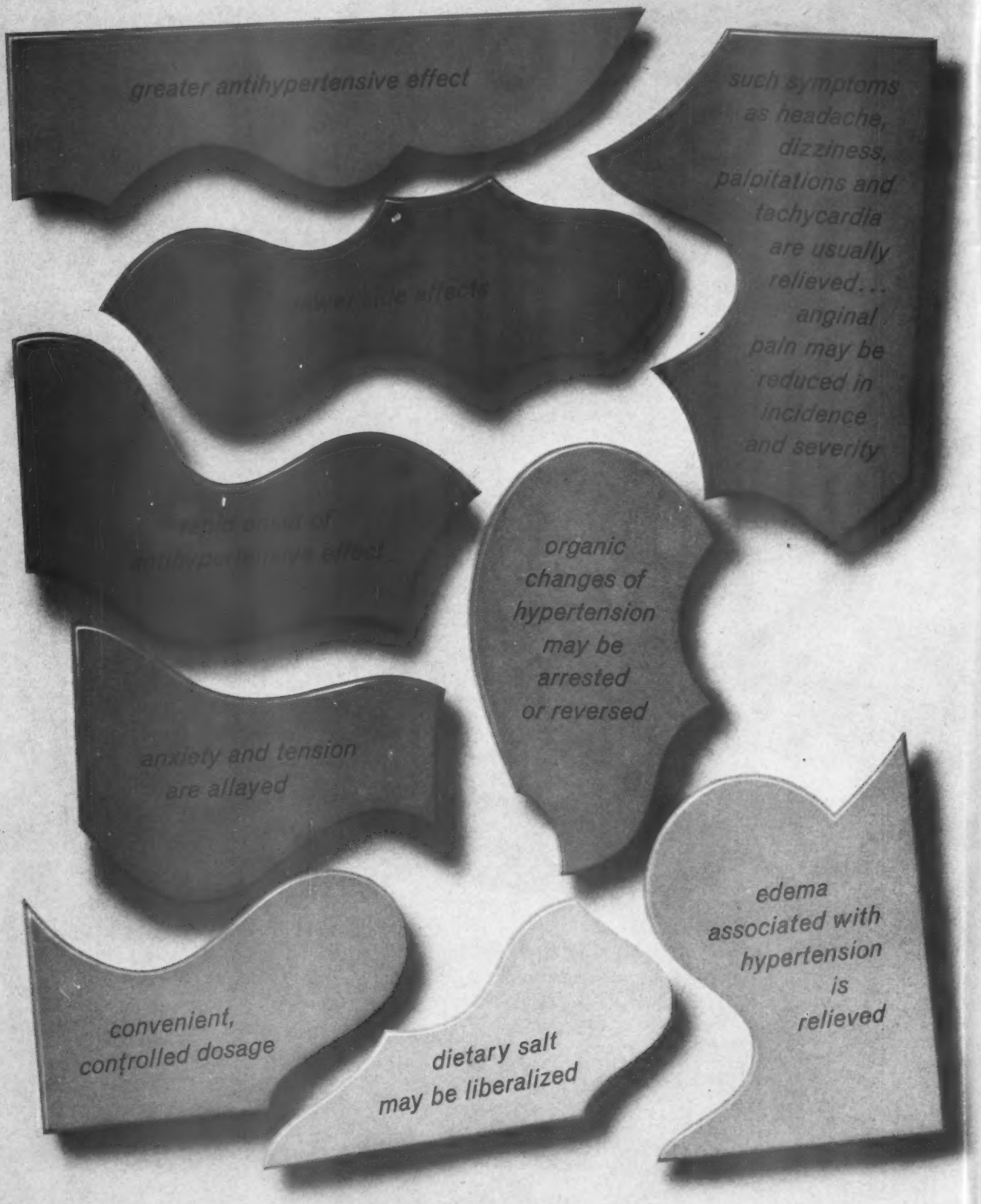
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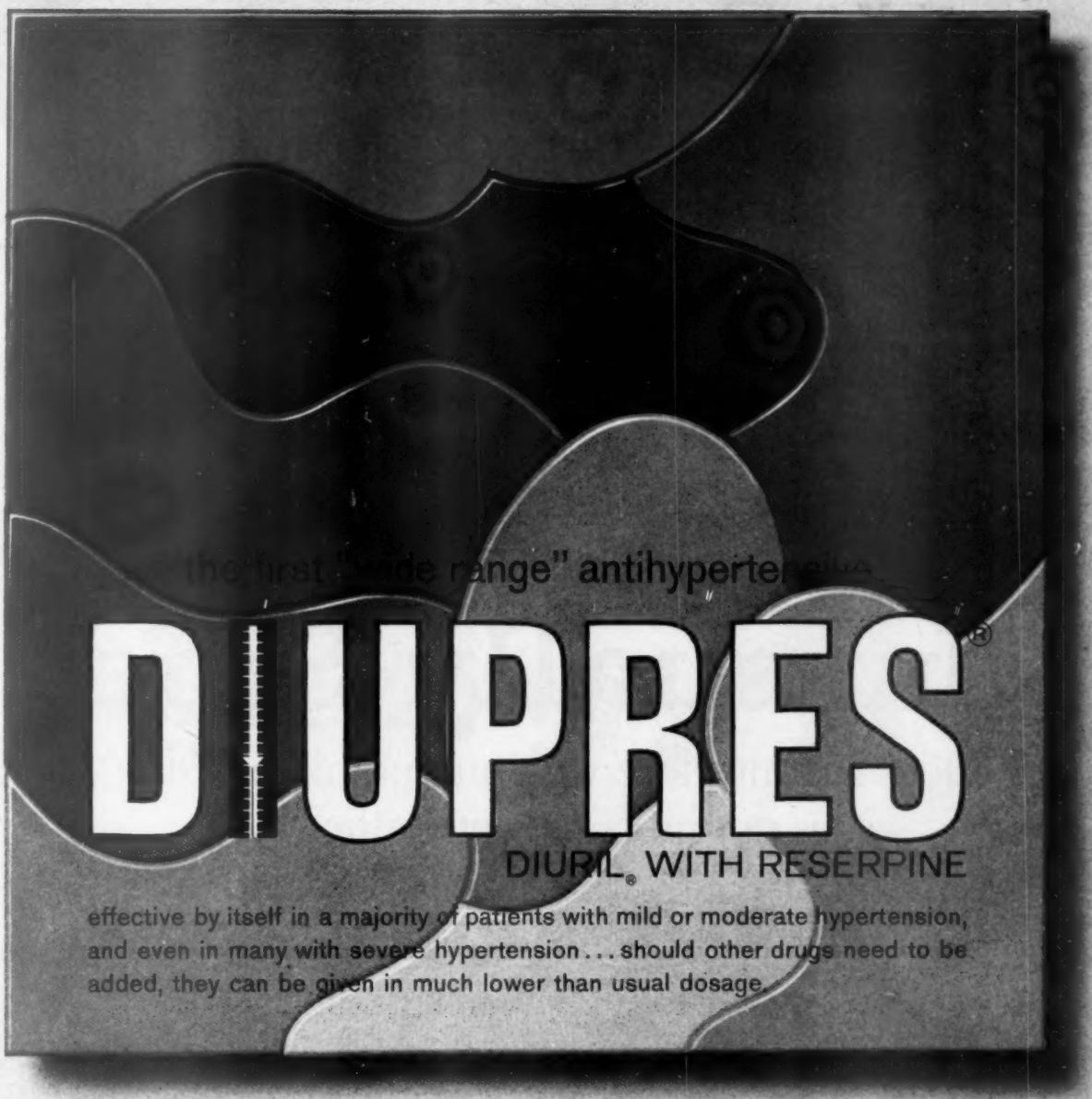
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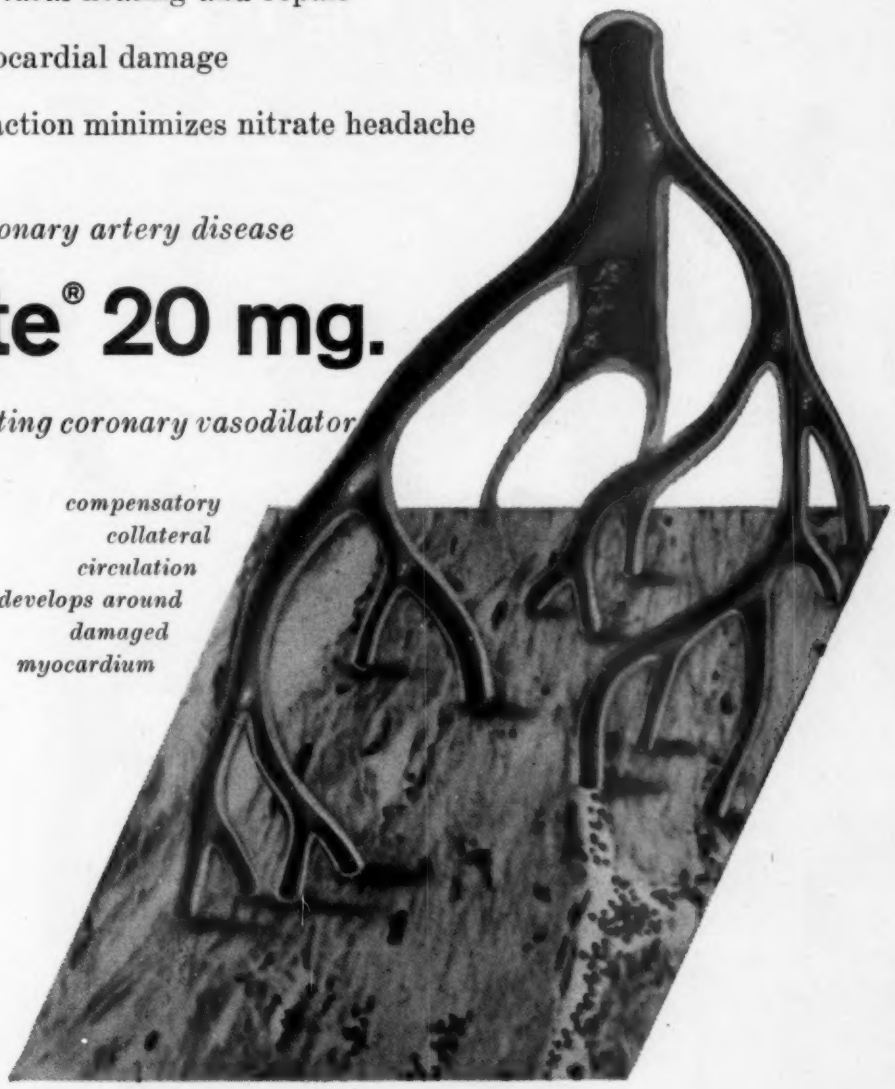

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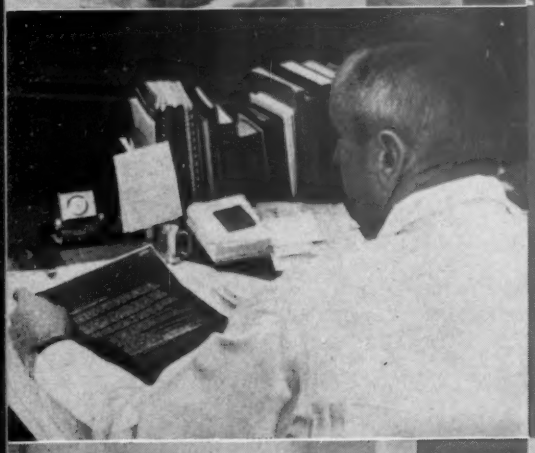

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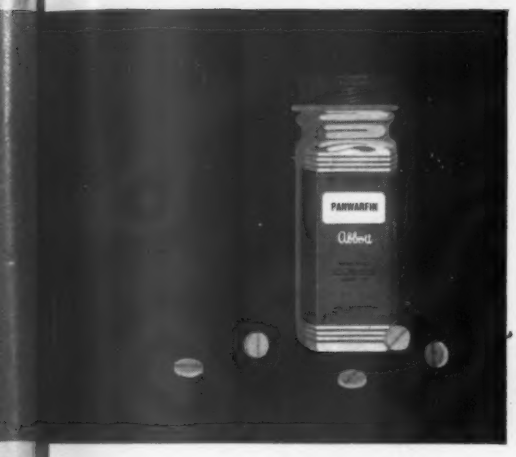

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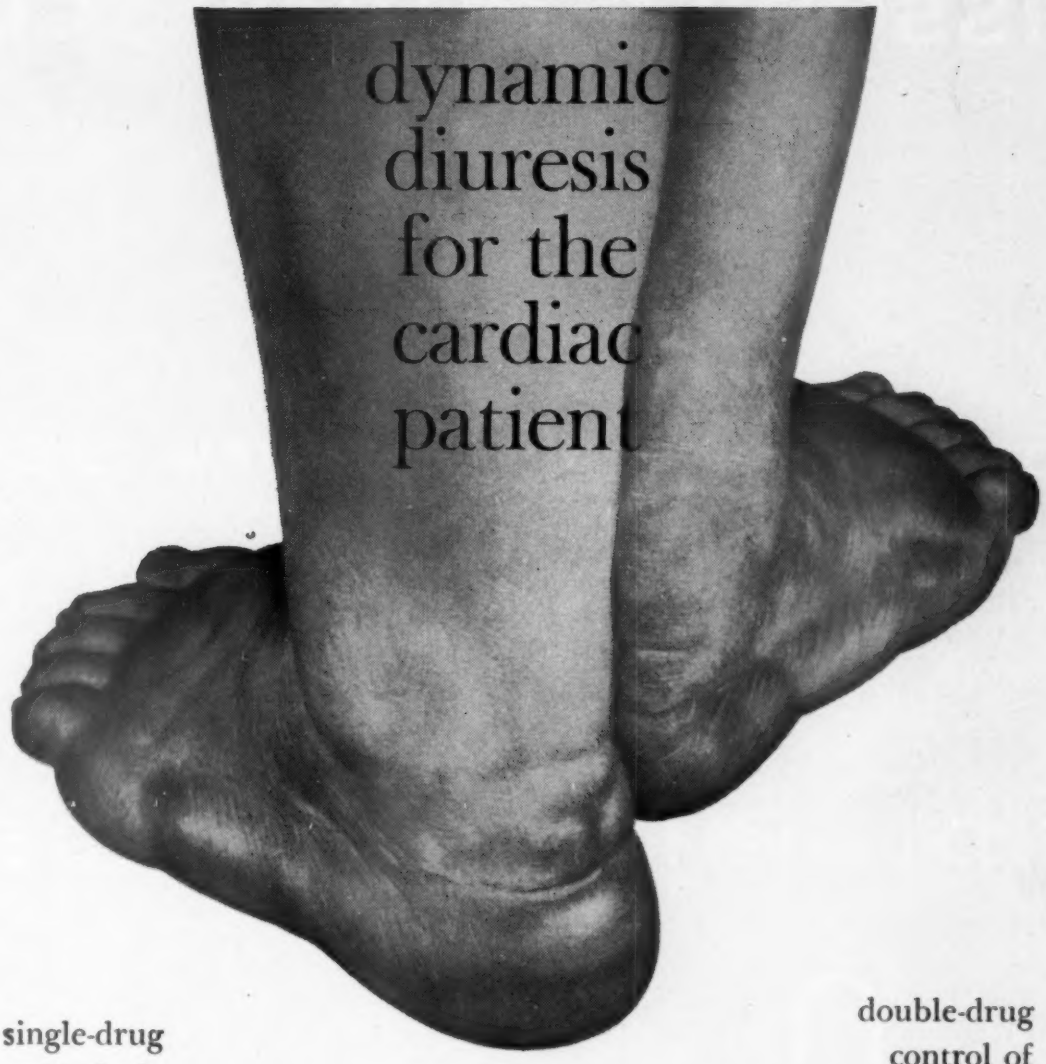

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1. Moser, K.M.: J.A.M.A. *167*:1695 (Aug. 2) 1958.
2. Cliffton, E.E.: J. Am. Geriatrics Soc. *6*:118, 1958.
3. Sussman, B.J., and Fitch, T.S.P.: J.A.M.A. *167*:1705 (Aug. 2) 1958.
4. Singher, H.O., and Chapple, R.V.: Clin. Med. *6*:439 (March) 1959.

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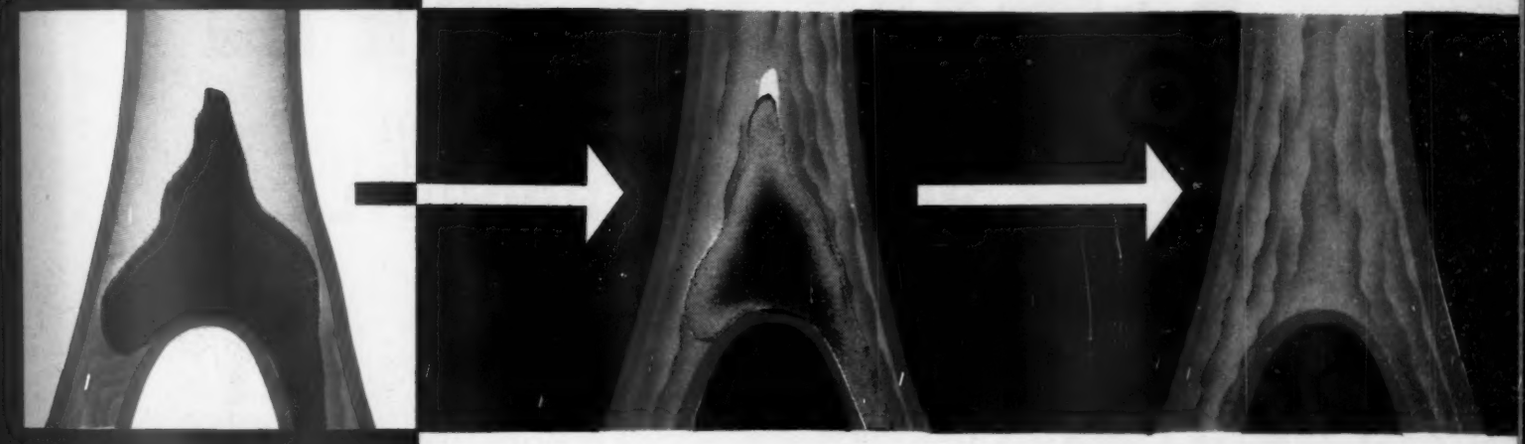

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1. Riseman, J.E.F., *et al.*: Circulation *17*:22 (Jan.) 1958.

2. Russek, H.I.: Circulation *18*:774 (Oct.) 1958.

3. Hirshleifer, I., *et al.*: Scientific Exhibit, A.M.A., Atlantic City, N. J., June, 1959.

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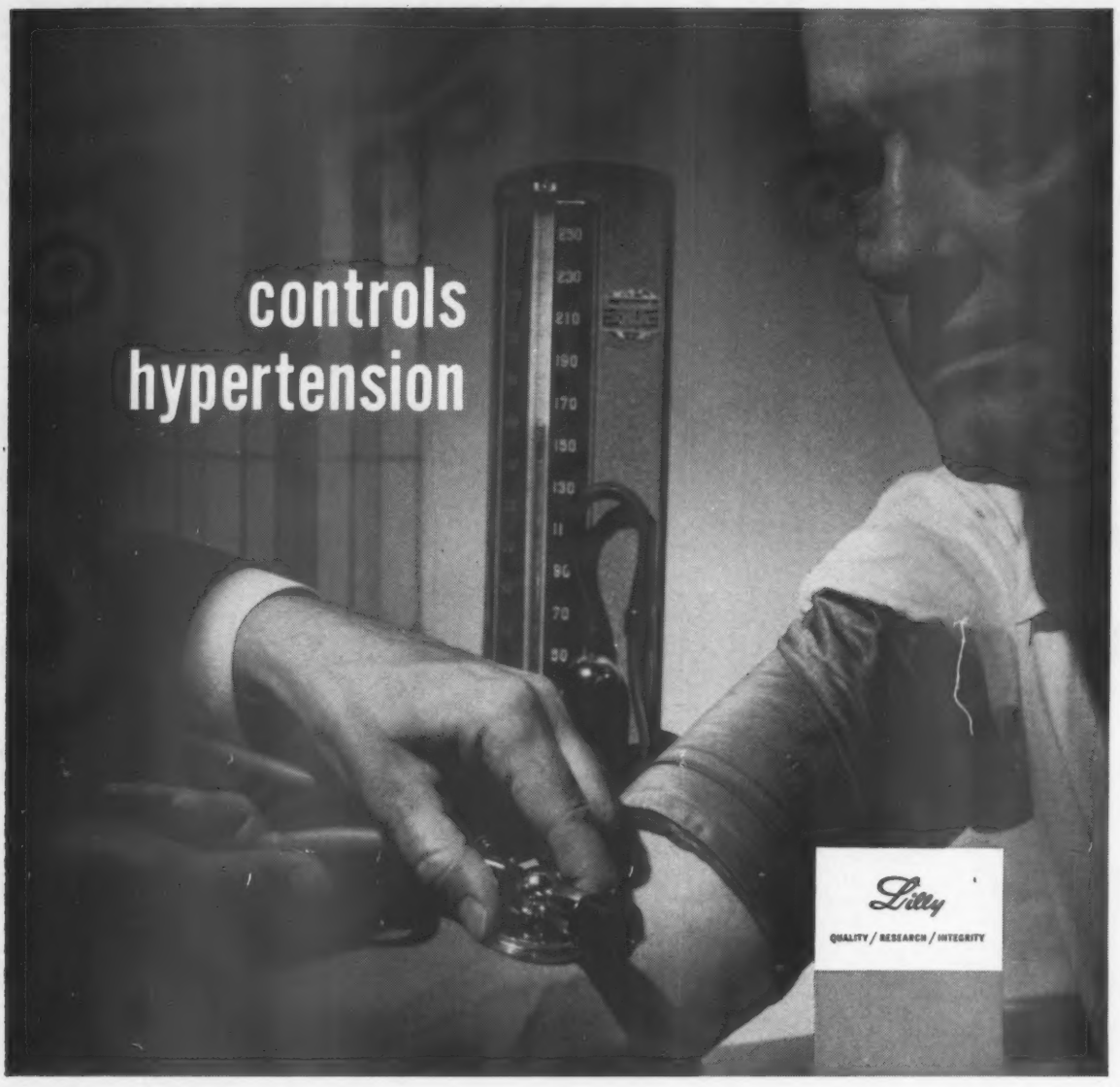

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1. Geriatrics, *12*:185, 1957.
2. J. Indiana M.A., *48*:603, 1955.

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The American Journal of Cardiology

VOLUME V MARCH 1960 NUMBER 3

EDITORIAL

The Hemodynamic Concept of Atherosclerosis

BARRIERS to the advancement of knowledge in medical science are being surmounted by the application of basic sciences. Modern medical practice utilizes basic scientific facts established by many disciplines. Atomic physicists, chemists and engineers are contributing their knowledge to medical research and thus to clinical medicine. The fields of nuclear physics and enzyme chemistry applied to the human body are examples of the expanding integration of knowledge. The crossing of lines which arbitrarily divide the sciences enriches both the donor and the recipient discipline. Such cross fertilization must be encouraged if solution rather than stagnation of research problems in medical science is to be achieved.

The hemodynamic concept of atherosclerosis[1,3] considers the laws of fluid dynamics as the primary factor in the etiology of atherosclerosis. Atherosclerosis has been experimentally produced[2,4] and can be proved to be primarily a sequel of fluid mechanics applied to the natural conditions in the circulatory system. It now appears established that the laws of fluid dynamics account for the localization of atherosclerotic lesions as well as the progressive pathologic changes at specific areas of predilection. Such locations are subject to a relative decrease in local lateral pressure in accordance with the nature of the motion of fluids, in this case the blood. The areas of predilection are characterized by curvature, bifurcation, branching, tapering or external attachment. The variations in the severity of atherosclerosis among individual patients appear to be due principally to individual differences in hydraulic specifications. The velocity of blood flow, the caliber of the lumen and the anatomic pattern have a composite hydraulic effect which determines the sites of predilection and the progressive changes which may follow. A biologic factor must also be considered, namely, the local reparative reaction of the wall of the vessel, expecially the intima. Differences in biologic response to injury and differences in tissue or fabric structure as well as species differences may determine the nature and degree of atherosclerotic change. The contributing atherogenic effects of other factors such as age, sex, race, diet, nutritional status, lipid metabolism, drugs, hormones, associated disease, hypertension and stress require re-evaluation as secondary factors. It is suggested that these factors may merely modify the primary hemodynamic mechanism.

The hemodynamic concept of atherosclerosis was developed by correlating atherosclerotic lesions found at autopsy with their localization as determined by hydraulic principles. It was then demonstrated with the aid of model hydraulic systems built to the precise specifications of blood vessels obtained at autopsy. Flow in these models, as well as in the arterial tree generally, is streamline or laminar rather than turbulent. The forces and principles involved are directly comparable to those which prevail in all hydraulic systems. The flow of rivers and streams in their boundaries, the flight of the airplane, the insect and the bird, the movement of a ship in the water or a fish in the depths and the circulation of the blood in our arteries and veins are in major degree varied expressions of the laws of fluid mechanics. Everywhere in this domain, the laws of fluid mechanics must control.

Sites of predilection for atherosclerosis can be predicted by the same methods used by hy-

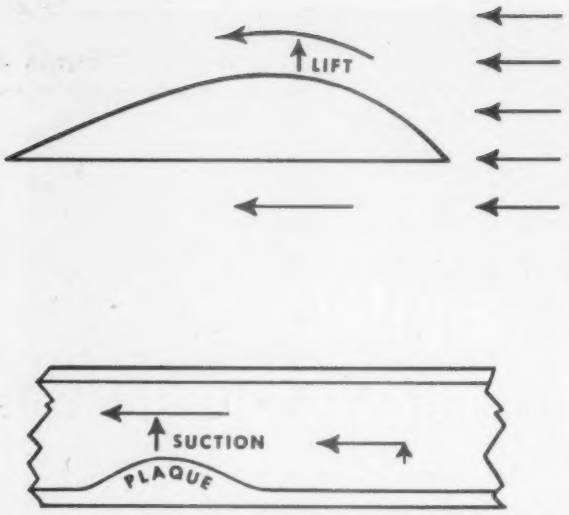

FIG. 1. Similarity of dynamic factors involving an airfoil and an atherosclerotic plaque. *Upper*, airfoil lift due to increased air velocity. *Lower*, velocity and pressure changes (suction) associated with atherosclerotic plaque. (Figures 1 through 3 from TEXON, M. *Arch. Int. Med.*, 99: 418, 1957.[1])

draulic engineers. The published study[1] of 100 consecutive patients who came to autopsy confirms the predilection of atherosclerotic lesions for the exact sites determined by the laws of fluid mechanics. Atherosclerosis in man begins with a minute alteration, a lifting of the endothelium and thickening of the intima by proliferation of fibroblasts. Both the initial stimulus and the increasingly serious progression of the lesion are readily understood in terms of Bernoulli's theorem ($V_1 + P_1^2 = V_2 + P_2^2$). Stated simply, Bernoulli's theorem holds that fluid in motion possesses energy by virtue of its velocity and its lateral, or static pressure. The sum of the energy due to velocity and the energy due to lateral pressure is constant at any two points of flow, provided no energy is lost between them.

A familiar application of this theorem occurs

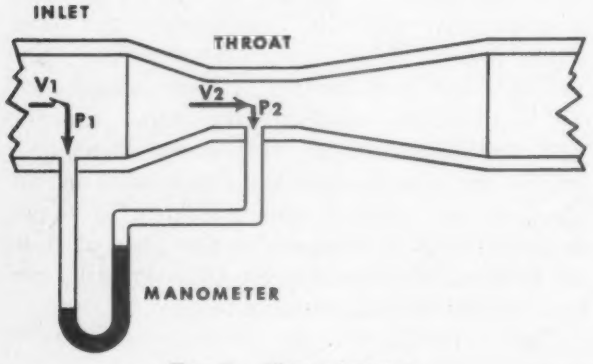

FIG. 2. Venturi meter.

FIG. 3. Elbow flow meter.

in the flight of an airplane (Fig. 1). The reduction in pressure caused by the greater velocity of air traveling over the curved top surface of the wing creates the lift which makes flight possible. In the human arterial system at sites of relative reduction in lateral pressure, this same lift tends to draw the walls of the vessel inward toward the center of the lumen and it is precisely at these sites that atherosclerosis begins.

Pathologists have long noticed the frequent occurrence of atherosclerotic lesions in arteries which taper, curve and branch or bifurcate. In each of these situations Bernoulli's theorem is directly applicable. An understanding of the application of Bernoulli's theorem clearly refutes the notion that atherosclerosis is a "patchy" disease occurring at haphazard or unpredictable areas.

(1) The tapering blood vessel is analogous to a Venturi meter (Fig. 2). Where the walls converge or taper the velocity increases and lateral pressure decreases. The local decrease in lateral pressure produces, in effect, a "suction action." The endothelium and cells of the intima are lifted. This calls forth the initial reparative reaction of intimal thickening by fibrous tissue proliferation, the first step toward the formation of a well defined atherosclerotic plaque.

(2) A similar effect accounts for the localization of atherosclerotic lesions at areas of curvature. The mechanical forces involved are demonstrated in an elbow flow meter (Fig. 3).

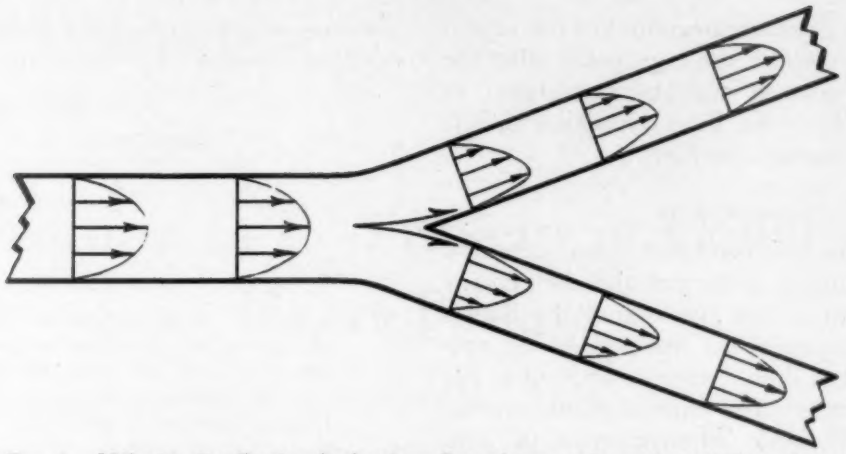

FIG. 4. Velocity distribution for laminar flow along a tube and at a bifurcation. (From: TEXON, M., IMPARATO, A. and LORD, J. W. *Arch. Surg.*, 80: 47, 1960.[2])

In this case, lateral pressure is increased along the outer curvature and decreased along the inner curvature due to centrifugal force. Thus, the site of relative reduction in lateral pressure in a curving blood vessel is on the inner curvature. It is here, as expected, that the intima thickens and the atherosclerotic plaque develops.

(3) Finally, since the velocity of flow at the cross section of a tube increases from the wall toward the center, division of the more central or axial stream at the site of branching or bifurcation (Fig. 4) results in a relative increase in velocity and a relative decrease in lateral pressure at the medial walls of the crotch zone. Similar hydraulic conditions are found in the circulatory system wherever vessels branch or bifurcate, e.g., where the aorta divides to form the common iliac arteries.

(4) At areas of external attachment, as on the dorsal wall of the thoracic aorta, the predilection for atherosclerosis is further enhanced.

The hemodynamic concept applies to the circulation in the aorta and coronary arteries as well as to the arteries of the viscera and extremities. It also applies to the pulmonary artery and the venous circulation generally.

Experimental Proof of Hemodynamic Concept: An approach to scientific proof that the laws of fluid dynamics are the primary factor in the etiology and pathogenesis of atherosclerosis has been achieved by altering hydraulic specification under controlled conditions in order to observe changes in the arterial wall. This has been done in dogs on a normal diet by excising a portion of the carotid artery and interposing it as an autograft at the transected femoral artery. The femoral artery became elongated by the autograft and assumed an S-shaped configuration. After an interval of six months, the elongated S-shaped femoral artery including the autograft of the carotid artery was examined and found to be patent and pulsating. The curves were identified, photographed, excised and examined histologically. Other dogs on a normal diet and with similar surgically produced S-shaped curvatures were examined after a twelve-month interval. Changes in the arterial wall were observed after six months at the internal curvatures of the S-shaped autograft. The vascular change appeared to consist of a thickening of the media due to muscular proliferation and hypertrophy with separation of elastic fibers. Changes in the arterial wall after twelve months consisted of intimal thickening by fibrous tissue proliferation (Fig. 5). The plaque was found to be

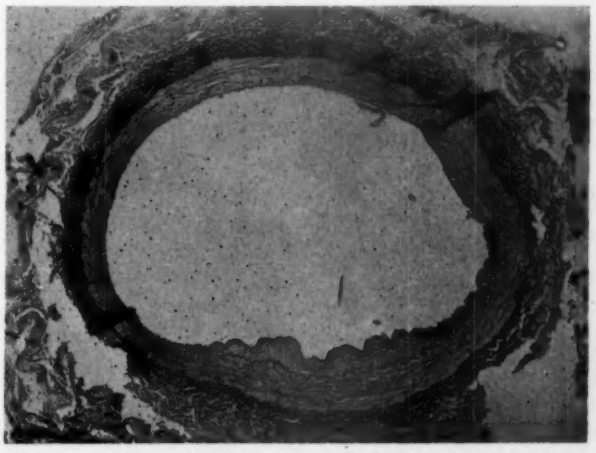

FIG. 5. Atherosclerotic plaque at site of surgically produced curvature in dog's femoral artery. The crescentic shaped plaque is localized at the internal curvature (see text).

localized at the internal curvatures of the vessel. These findings compel the conclusion that the atherosclerotic plaque must be considered to be due primarily to the fluid dynamics, in this case the laws of curvilinear flow.

Conclusions

On the basis of correlated data obtained from human autopsy specimens and the demonstration of the applicable laws of fluid mechanics in models, atherosclerosis appears to be primarily a sequel of fluid dynamics applied to the circulatory system. The experimental production of hemodynamic atherosclerosis in dogs further corroborates the concept that hemodynamics is the primary factor in the etiology and pathogenesis of atherosclerosis. The data adduced are conclusive. It is hoped that this breakthrough in identifying the primary cause of atherosclerosis will also lead to specific therapy or prevention, the ultimate goal of all medical science.

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Clinical Studies

Absorption of I^{131}-Triolein in Congestive Heart Failure

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IT HAS BEEN known for some time that congestive heart failure of long duration will result in impairment of the patient's general condition and sometimes in development of cachexia. Comparatively little study has been focused so far on the reasons leading to the undernourishment of patients with heart failure.

According to investigations carried out by Harrison,[1] undernourishment associated with congestive heart failure is partly due to anorexia. For this reason a low caloric intake is a common finding in patients with heart failure. Furthermore, the caloric deficiency is accentuated by the high metabolic rate common in these patients. The anorexia may be a result of a disturbed intestinal motor function, which in association with mild tissue anoxia manifests itself as decreased hunger contractions, depressed intestinal tone, weakened peristalsis and delayed emptying of the stomach.[2]

Surprisingly little attention has been attached to the possibility of a reduced absorption of different foods in congestive heart failure, which may be a factor contributing to the poor nutritional state. The literature apparently contains only the investigation by Hardy and Schultz[3] in which they demonstrated a retarded absorption of amino acids from the jejunum in patients with edema. While this report was being written, Berkowitz et al.[4] published their studies on fat absorption in various diseases and presented preliminary data on the absorption of I^{131}-triolein into the blood in congestive heart failure.

The purpose of our investigation was to study the absorption of fat in congestive heart failure, using triolein labeled with radioactive iodine (I^{131}). In addition to the absorption of fat into the blood, the amount of fat excreted in the feces was also studied.

MATERIAL AND METHODS

I^{131}-labeled triolein was prepared according to the method of Lubran and Pearson,[5] and 30 to 50 μc. of the I^{131}-triolein (0.05 to 0.25 cc.) was included in a fat meal containing 0.5 gm. of olive oil per kg. of body weight and 2 cc. of Tween 80 as emulsifier. Subjects were fasted for twelve hours prior to administration of the test meal and for six hours after its ingestion. Lugol's solution was given to prevent the accumulation of radioactive iodine in the thyroid gland.

Samples of venous blood were drawn from the subjects two, four, five and six hours after administration of the fat meal. The lipid-bound activity in the blood precipitated with trichloracetic acid was determined from the blood samples by the method of Beres et al.,[6] using a scintillation crystal well counter (Nuclear, Chicago, Ill.).

Following the fat meal the stools were collected for three days; special care was taken to avoid contamination with urine. In the case of obstipation collection was continued until three stools had been obtained. For determination of the radioactivity of the feces the vessel containing the stools was placed at a distance of 10 cm. from the scintillation counter (Frieseke-Hoepfner, Erlangen-Bruck, West Germany) and the result was compared with that of a similarly counted standard solution. The results obtained from the samples of blood and feces were expressed as percentages of the administered dose. The total blood volume was assessed at 7.2 per cent of the body weight.

The absorption of labeled triolein was studied in twelve subjects, mean age forty-six years (range twenty-six to sixty-five years), who were hospitalized for observation and in whom no gastrointestinal

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TABLE I

The Lipid-Bound Activity of Blood and Fecal Excretion of Isotope after a Fat Meal with I^{131}-Labeled Triolein in Patients with Congestive Heart Failure

Case No.	Age (yr.)	Etiology of Congestive Heart Failure	Degree of Heart Failure			I^{131}-Activity as Percentage of Dose				
			Edema	Enlarged Liver	Pulmonary Stasis	In Feces	In Blood (hr.)			
							2	4	5	6
1	63	Myocardial infarction	+	++	+	100.0	0	0	0	0
2	50	Etiology unknown	+	+	+	72.4	0.1	0.7	2.0	4.4
3	52	Carcinoid syndrome	++	+	+	64.8	0.0	0.0	0.0	1.3
			(...)	(...)	(...)	(14.7)	(1.8)	(3.6)	(1.9)	(1.2)
4	51	Aortic stenosis	++	+	+	54.6	0.0	0.0	0.0	0.0
5	62	Myocardial infarction	+++	+	+	41.4	1.4	1.9	1.6	1.4
6	74	Cor pulmonale	++	+	+	38.9	0.7	0.0	0.0	0.0
			(+)	(+)	(+)	(20.4)	(0.3)	(1.5)	(1.4)	(1.2)
7	64	Myocardial infarction	+	+	+	37.5	0.4	0.3	0.6	0.0
			(...)	(...)	(...)	(2.7)	(1.5)	(2.7)	(3.9)	(2.3)
8	55	Hypertensive heart disease	+	+	+	30.8	0.0	3.3	3.1	0.1
9	72	Aortic stenosis	+	+	+	29.0	0.0	0.7	1.3	0.7
10	64	Myocardial infarction	+	...	+	24.9	0.4	1.7	2.2	1.2
11	83	Etiology unknown	++	+	+	17.5	0.3	0.0	0.0	0.0
12	48	Hypertensive heart disease	...	+	++	17.1	1.0	1.1	0.9	1.6
13	52	Atrial septal defect	...	+	+	15.9	1.3	1.1	1.7	5.2
14	69	Rheumatic heart disease	...	+	+	12.3	1.2	1.3	1.2	6.0
15	61	Aortic stenosis	...	...	+	3.6	1.3	2.6	3.3	2.2
16	42	Mitral stenosis	+	+	+	2.4	0.4	2.3	2.6	2.0
17	63	Rheumatic heart disease	...	...	...	2.4	1.0	1.8	2.4	0.0
Mean						30.2	0.7	1.3	1.5	1. 5

NOTE: Figures in parentheses represent values after treatment (Cases 3, 6 and 7).

disease or congestive heart failure was diagnosed. These were used as a control group.

To study fat absorption in congestive heart failure the fat meal was administered to seventeen patients. The etiology and severity of the heart failure in each of these patients are shown in Table I. They were found not to have any disease possibly influencing fat absorption, with the exception of one patient (Case 3), in whom a carcinoid syndrome was the etiologic factor of the heart failure. We are not aware of the possible effect of the carcinoid syndrome on fat absorption. Since it appeared at an early stage of the investigation that fat absorption is altered in patients with heart failure, further studies were carried out with three patients (Cases 3, 6 and 7) in order to find out whether fat absorption tends to become normalized as congestive heart failure becomes improved.

RESULTS

Blood Lipid Activity: In the control series of twelve subjects (Figs. 1 and 2) the mean lipid-bound activity in the blood was highest (3.8 per cent) in the sample drawn five hours after the fat meal.

As shown in Figure 1 and Table I, the fat test showed that the mean blood lipid activity

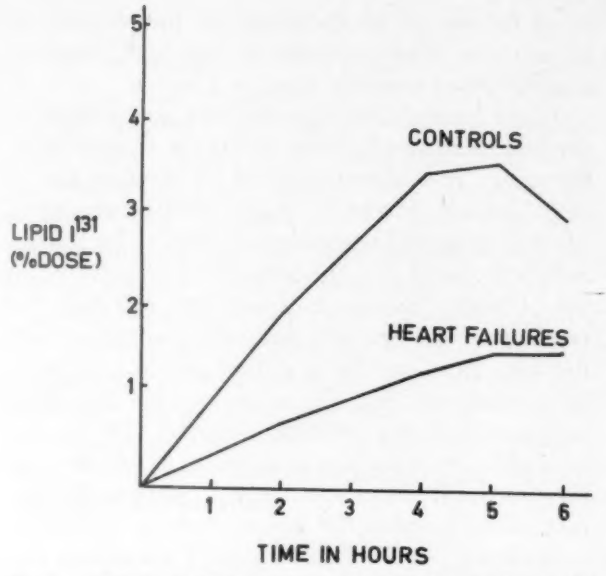

FIG. 1. Mean lipid-bound activity of blood after a fat meal with I^{131}-labeled triolein in twelve control subjects and in seventeen patients with congestive heart failure.

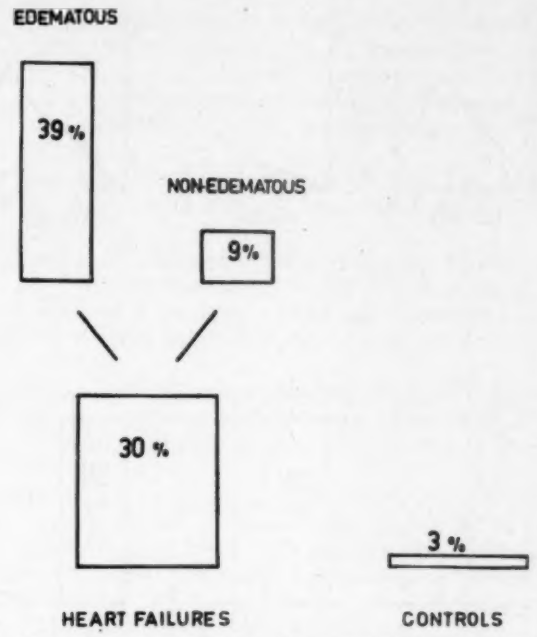

FIG. 2. Mean percentage of ingested isotope excreted in feces after a test meal with I^{131}-labeled triolein.

was definitely lower in the seventeen patients with congestive heart failure than in the control subjects, and reached its maximum (1.5 per cent) in the last sample taken six hours after the fat meal. Patients who had edema at the time of examination exhibited a lower activity than those without edema. Three patients (Cases 3, 6 and 7) who were re-examined after improvement in the heart failure exhibited a definitely higher level of activity in the blood than in the first test (Fig. 3). In two patients (Cases 1 and 4) the blood samples showed no activity. Both patients had severe congestive heart failure with edema. One of these patients excreted the entire fat dose in the feces within three days and the other patient excreted 54.6 per cent of the dose.

Fecal Fat Excretion: In the control subjects a mean of 2.7 per cent of the administered fat was eliminated in the feces during three days; about two-thirds of this amount was excreted during the first twenty-four hours and about one-sixth on each of the following two days. These observations are in agreement with the values obtained for healthy persons by other investigators.[6–8]

The feces collected during three days from the patients with heart failure showed a mean activity of 30.2 per cent of the administered dose. This is more than tenfold the amount excreted by the control subjects (Table I, Fig. 2). In the patients who had edema associated with heart failure (thirteen determinations) the mean percentage of fat excreted in the feces was definitely higher (39.1 per cent) than in patients with mild heart failure (four patients, 9.4 per cent, Fig. 2). In four patients (Cases 7, 15, 16 and 17) the excretion of fecal fat was in the normal range (<4 per cent). In three of these patients (Cases 7, 15 and 17) the congestive heart failure was very mild at the time of testing. The blood activity curve of these three patients was near the normal level of absorption.

The three patients (Cases 3, 6 and 7) who were mentioned before in discussing the blood activity values showed a decreased activity in the feces in the repeated test (Fig. 3). In one patient (Case 7) the heart failure was compensated and the percentage of fecal activity in the repeated fat test had declined from 37.3 per cent to the normal level of 2.7 per cent.

As was the case also in the control series the greater part of the excreted activity in the patients with congestive heart failure was present in the stools on the first day, while the stools on the second and third day usually contained only 10 to 20 per cent of the total fecal excretion of fat.

Blood Cholesterol Levels: Although it is difficult to draw conclusions concerning the blood cholesterol values from this small series of patients, it was interesting to observe that in patients with congestive heart failure whose fecal excretion of fat was below the mean level of 30

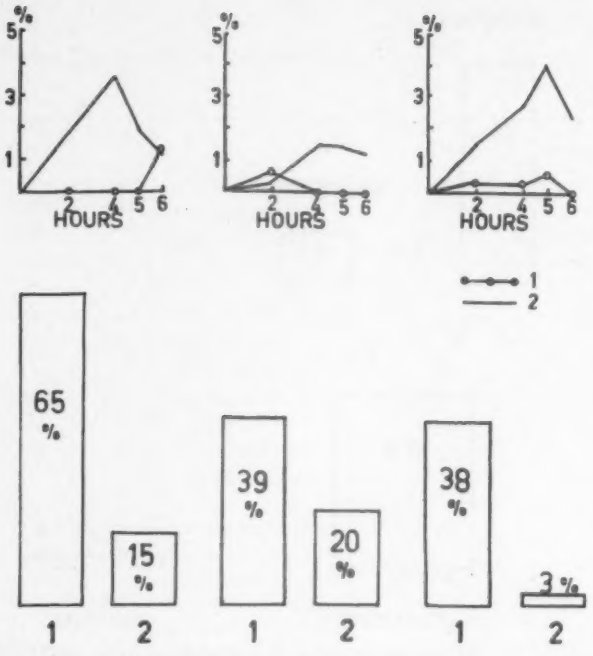

FIG. 3. Lipid-bound activity of blood and fecal excretion of isotope after a test meal with I^{131}-triolein in three patients with congestive heart failure. (1) At beginning of treatment. (2) After improvement in the state of the heart failure.

per cent of the administered dose, the mean cholesterol value was 225 mg. per cent, and that patients having a fat excretion above the mean level had a definitely lower mean blood cholesterol value (151 mg. per cent). Studies on patients with coronary atherosclerosis and hypercholesteremia indicate also that there may be a relation between the absorption of fat and the blood cholesterol.[9]

COMMENTS

It has previously been demonstrated that the use of I^{131}-labeled fats in the study of fat absorption is a reliable method and gives results comparable to those obtained by the more difficult and time-consuming chemical analysis of fats.[10–12] It has been observed, however, that the use of I^{131}-triolein can give also lower blood values than the chemical method.[13]

The results reported above show that the lipid-bound activity in the blood is clearly decreased and retarded in patients with congestive heart failure, as compared with control subjects, and that with improvement in the state of heart failure the absorption of fat definitely increases.

Causes of Low Lipid Levels in Blood: The low activity level in the blood may be due, among other factors, to an increased fat metabolism or to a more rapid storage of fats. A lowered absorption of fat may also be a factor.

When these various possibilities are evaluated, the last mentioned factor seems the most plausible one. It is also supported by the fact that a large amount of the fat is excreted in the feces. Merely delayed absorption appears to be hardly sufficient cause for the low level of activity in the blood. Evidence speaking against the possibility of a greatly delayed absorption was the fact that on the first day about the same proportion of total fat was excreted by these patients and the normal subjects. It is not possible to express any opinion as to whether an increased fat metabolism or a higher storage rate contributed to the low activity in the blood.

Berkowitz et al.[4] have recently published observations according to which the blood activity curve following the administration of I^{131}-triolein is low in patients with congestive heart failure and reverts to normal when the heart failure is compensated. They suggested that this is due to deficient absorption of fat, but published no detailed data of their results.

Causes of Deficient Fat Absorption in Heart Failure: It is evident that deficient absorption of fat is in some way related to heart failure, as is indicated by the fact that disturbance in absorption of fat appears to be correlated with the degree of congestive heart failure and that it improves as the heart failure becomes compensated. There is at present no knowledge concerning the factors causing the lowered absorption of fat in congestive heart failure. As possible factors may be suggested, for example, a reduced secretion into the intestines of enzymes and emulsifiers necessary for absorption of fat, edema of the intestinal mucosa and possibly an impaired mixing of the intestinal contents because of depressed tone and peristalsis.

The observations presented refer to the absorption of triolein only. It has been demonstrated earlier that the absorption of I^{131}-oleic acid differs from that of I^{131}-triolein.[4,7,14] The absorption of oleic acid in congestive heart failure is of interest, and a study of this subject is in progress.

The reduced absorption of fats may be a significant factor in the loss of weight by patients with congestive heart failure. In this connection one must not disregard the fact, brought out by recent investigations, that fats play an important role in the metabolism of the heart muscle.[15,16]

Summary

The absorption of I^{131}-triolein into the blood and the fecal excretion of I^{131} activity were studied in seventeen patients with congestive heart failure and twelve control subjects with no congestive heart failure or gastrointestinal disease. The recovery of I^{131}-lipid was distinctly smaller and the peak activity occurred later in patients with heart failure than in control subjects. The fecal excretion of radioactivity by these patients after the ingestion of I^{131}-triolein was several times the radioactivity excreted by the control subjects. The changes were greatest in patients with severe congestive heart failure and improved as the heart failure became compensated.

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Cardiac Adrenergic Preponderance Due to Lack of Physical Exercise and Its Pathogenic Implications*

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LACK of physical exercise, resulting from motorization, automation, television-sitting, and from the nearly universal availability of a multitude of labor-saving devices, has become one of the most conspicuous characteristics of 20th century Western civilization. Among its various ill effects on physical and mental health,[1] those concerning the cardiovascular system have received particularly wide attention in recent years. Next to the long suspected causal role of a high dietary fat and cholesterol intake in atherogenesis,[2–6] the lack of physical exercise has been accused of enhancing the development of degenerative heart disease and, thus, of materially contributing to the cardiac death rate in Western countries.[7–14c]

Curiously, despite the widespread discussion of this phenomenon and of its statistical evidence, only few attempts have been made so far to elucidate its pathophysiological background. Some experimental observations suggest a favorable influence of exercise on the development of the coronary vascular network[15,16] in apparent analogy to that of the striated muscles.[17] Furthermore, in exercised, cholesterol-fed animals, the blood cholesterol level was found lowered and the incidence of atherosclerotic lesions appeared reduced.[18–20,97] However, in man, the serum cholesterol did not seem to be significantly affected by physical training;[21] some observations[135] suggest even an aggravation of coronary atherogenesis in exercised cholesterol-fed animals. Clinical evidence of existing atherosclerosis appeared higher in 300 middle-aged sedentary individuals, compared with an equal number of athletes.[22]

While these findings are of interest with regard to problems of the myocardial vascular blood supply and its important pathogenic implications, it should be kept in mind that the coexistence or even the exclusive presence of primary neurohormone and hormone-induced biochemical lesions of the myocardial fibers likewise plays an outstanding role in myocardial degeneration, necrotization and ultimate failure.[23–26d] Similar neurohormonal-hormonal influences contribute to the deposition of excess lipids in the arterial walls.[27]

The cardiac vagal tone of highly trained endurance athletes has often been described as being markedly elevated, causing a slow heart rate and high efficiency of the heart muscle.[28–36] On the other hand, persons with degenerative (hypertensive and/or arteriosclerotic) heart disease and those with subendocardial fibrosis of an apparently purely metabolic origin[37] ordinarily display signs of adrenergic (sympathetic) preponderance: accelerated heart action, especially with muscular effort, hypoxic changes in the electrocardiogram, and reduced cardiac efficiency,[38] all features resembling those which are elicited by the administration of epinephrine or by cardiac sympathetic stimulation. By contrast, nearly all effective therapeutic procedures

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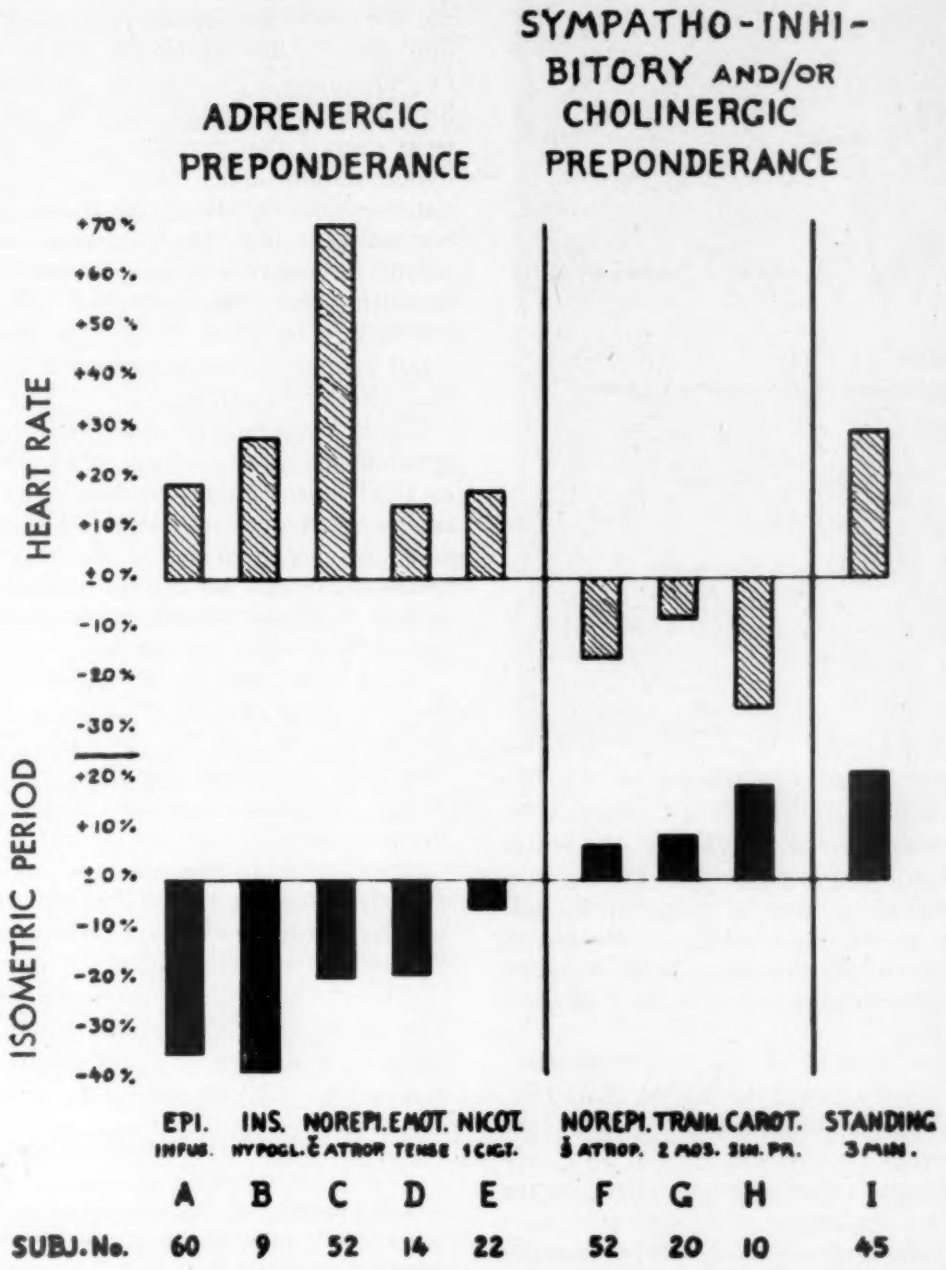

FIG. 1. Average responses of heart rate and isometric period to: A, *epinephrine infusion* (0.1 γ/kg./minute). B, *insulin hypoglycemia* (epinephrine discharge) (average 22 units). C, *norepinephrine infusion* (0.1 γ/kg./minute) after elimination of vagus reflexes by atropine (0.025 mg./kg.). D, *emotional tension* (students immediately before examination). E, *nicotine* (smoking one cigarette). F, *norepinephrine infusion* (0.1 γ/kg./minute) (reflex stimulation of cardiac vagus via pressoreceptors). G, *physical training* during average two months (running, gymnastics). H, *digital carotid sinus pressure* (fourth and fifth heart beat after beginning of pressure). I, *standing* during three minutes (decreased ventricular filling).

against angina pectoris, hypertensive heart disease and congestive cardiac failure are essentially antiadrenergic and/or procholinergic (catecholamine-reducing sympathectomy, ganglionic blockade, x-ray radiation of the adrenals, reserpine, catecholamine-inactivating thyrostatic drugs, paradoxically antiadrenergic iproniazid, vagus-stimulating carotid sinus pressure and morphine, and vagus-like acting digitalis).

In view of the potentially pathogenic cardiac effects of adrenergic overactivity, which sharply contrast with the advantages of the cholinergic preponderance and/or sympathetic inhibition of the trained athlete's heart, it appeared of interest to study the basic adrenergic-cholinergic equilibrium in groups of healthy subjects with

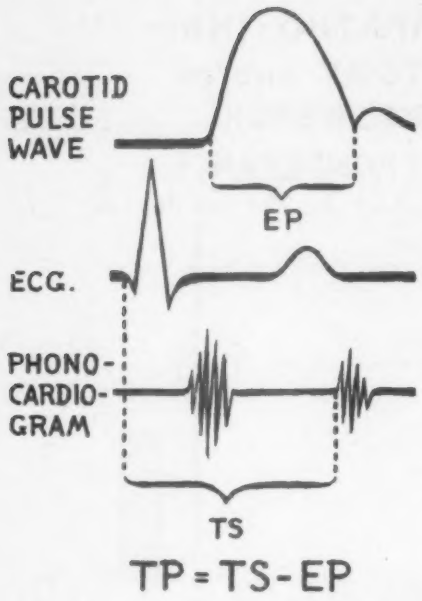

FIG. 2. Chronodynogram. EP = isotonic or ejection period. TS = total systole. TP = isometric or tension period.

different living habits. We intended to ascertain a possible influence of the degree of habitual physical activity and inactivity, respectively, on the neurohormonal regulation of cardiac dynamics at rest and in response to certain neurovegetative drugs (atropine, epinephrine, norepinephrine, given singly and combined). A separate group of persons was also to be tested before and after termination of limited physical training periods.

As primary criteria of the neurovegetative state of the heart we used the resting heart rate, representing chronotropic, and the length of the isometric period (= tension period, TP), representing inotropic neurovegetative effects on the left ventricle. The length of TP (see also under "Methods") is characteristically shortened under positive inotropic (adrenergic[39–51]) influences and lengthened under negative inotropic (cholinergic and/or sympatho-inhibitory[39,51a–55]) influences (Fig. 1), independent of heart rate[39,43,51a, 56–69] and of peripheral resistance, as demonstrated on the isolated heart with constant rate and filling pressure,[49,59] and on the heart *in situ*.[39]

Although the prolongation of TP in athletes is generally interpreted as the expression of a negative inotropic vagal action on the left ventricle, the existence of negative inotropic influences upon the ventricular myocardium remains problematic in view of the fact that the ventricles are devoid of vagal nervous fibers.[24] Whether or not the autochthonus non-neurogenic acetylcholine stores of the ventricular tissue[24] participate in "cholinergic" functional patterns has not been definitely established. Recent investigations suggest that certain cerebral cortical and hypothalamic areas are responsible for sympatho-inhibitory effects on the heart.[129] It is not unlikely that they are more directly involved in negative inotropic reactions of the ventricles than the cardiac vagus. A clear distinction between sympatho-inhibitory and vagal excitatory mechanisms has not yet been made in the human heart.

Cardioacceleratory and cardioaugmentor sympathetic elements were recognized as early as 1882 and 1883 by Gaskell[130] and Pavlov,[131] and recently again by Randall,[132] as acting in relative independence of each other. This seems to account for certain quantitative divergences between chronotropic and inotropic sympathetic effects on the heart.

Aside from these neurovegetative influences, the only factor capable of significantly modifying the length of TP in the normal heart, are alterations of ventricular filling. A diminished filling lengthens, and an augmented filling shortens the TP.

The length of the ejection period (EP) is directly determined by the heart rate and ventricular filling[40,47,51a,60] and, therefore, is of lesser interest for the evaluation of specific neurovegetative action on ventricular contractility. The quotient EP/TP increases under adrenergic influence and decreases under cholinergic and/or sympatho-inhibitory influence.

METHODS AND MATERIALS

Analysis of the time elements of the dynamic systolic phases of the left ventricle of the human heart was carried out with the graphic method of Blumberger.[40]

The electrocardiogram (standard lead II and the chest leads which showed the earliest beginning of Q or R) was registered at a paper speed of 10 or 5 cm. per second (according to the machines used), together with the heart sounds recorded from the left side of the upper sternum, and the carotid pulse wave (in Burlington with a 4-channel Polyviso, Sanborn, Boston; in Innsbruck with a 6-channel Multiscriptor, Hellige, Freiburg i.Br.).

Measurements: Designated by us as "chronodynogram"[39] (Fig. 2), measurements are expressed in thousandths of a second. They represent averages of ten to twenty individual readings and concern (1) the total systole (TS) from the earliest beginning of Q (or, if no Q could be identified, from the beginning of R) to the first vibration of the second heart sound;

(2) the isotonic or ejection period (EP) from the beginning steep ascent of the carotid pulse wave to the bottom of its incisura; and (3) the isometric or tension period* (TP) which is calculated by subtracting EP from TS. Heart rates were recorded by means of the electrocardiogram, and blood pressure levels by the auscultatory method.

The cardiac stroke volume was estimated in thirty-eight instances before and after the administration of atropine by means of the simultaneously applied methods of Broemser and Ranke[61] and Wezler and Böger,[62] the results of which agreed within a range of 10 to 20 per cent.[63]

Basic conditions; catecholamine infusions before and after atropine: Basic measurements in 266 men between seventeen and thirty-four years of age and in ninety-four men between thirty-five and fifty years of age were started after at least fifteen minutes rest in recumbency and on empty stomach, or approximately two hours after a light meal. In 216 subjects in the younger age group, the measurements were repeated seven minutes after termination of an intravenous injection (lasting two minutes) of atropine sulfate (0.025 mg. per kg.). In seventy-five instances, l-epinephrine (Adrenalin®) and in sixty-four instances l-norepinephrine (Levophed®) was infused intravenously in 5 per cent glucose solutions before and after the administration of atropine, each during five minutes, in the dosage of 0.1 μg. per kg. per minute, and in the following sequence: Rest—norepinephrine—rest (ten to fifteen minutes)—epinephrine—rest (ten to fifteen minutes)—atropine—rest (seven minutes)—epinephrine—rest (ten to fifteen minutes)—norepinephrine. Accurate dosage was safeguarded by calibration of each venoclysis unit used for the infusions. The test subjects were unaware of the catecholamine solutions being switched on and off the three-way cannula through which plain glucose solution flowed during the intervals. The individually calculated infusion drop counts were controlled by synchronization with an electric metronome.

In eight subjects, the injection of atropine was repeated within seven minutes with a 50 per cent larger dose in order to check the degree of completeness of atropinization achieved with the standard dose of 0.025 mg. per kg. In sixty-seven subjects, measurements were also taken before and at the end of three-minute standing periods before and after the administration of atropine.

Classification of subjects: Only healthy men between seventeen and fifty years of age were subjected to the tests. The total number of 360 subjects was divided according to age into two groups, A (seventeen to thirty-four years of age) and B (thirty-five to fifty years of age), and each of these two groups was divided into four categories (I to IV), in accordance with exercise habits. Special attention was paid to the exercise history for the months immediately preceding the tests. For instance, when a highly trained sportsman had discontinued his regular physical activities three or more months ago, he was no longer placed in category I.

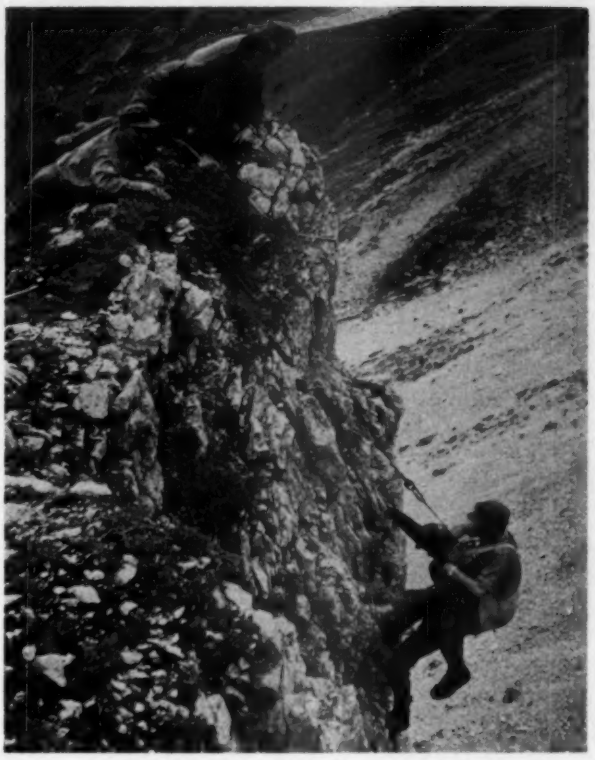

FIG. 3. Mountain rescue squad of Austrian Army (photograph by Federal Ministry of National Defense).

Within *category AI*, a subcategory AI+ was singled out which comprised only men engaged in competitive endurance sports (long distance running, cycling, swimming, skiing) but not strength and skill sports with lesser emphasis on endurance, such as wrestling, weight-lifting, judo, handball, basketball, soccer and ski downward racing. AI+ also included persons with exceptionally strenuous occupational activities (regular heavy load carrying in the Alps, heavy lumbering). Otherwise, category I of both age groups included men intensively and continuously but not competitively active in a variety of sports, soldiers in elite High Mountain Units of the Austrian army, members of mountain patrols (Austrian State Police and mountain rescue squads) (Fig. 3), peasants and laborers working on mountain farms.

Category II was composed of men with regular but lighter sports activities and in routine military training (including daily gymnastics), non-motorized farm laborers in the plains, and men on patrol duty

* The term "isometric" period is being used here as an equivalent of the German "Anspannungszeit." This comprises, beside the "isometric contraction period" as defined by Wiggers,[48] or "Druckanstiegszeit,"[64] also the preceding phase from the onset of the electrical systole to the onset of left ventricular pressure rise (Umformungszeit).[64]

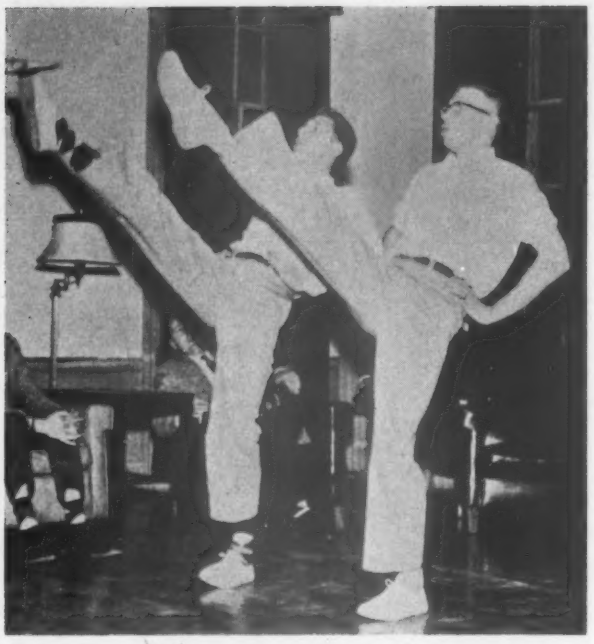

FIG. 4. Training for the "Kake-Walk," acrobatic dance competition.

in the plains, which included walking several hours every day.

Category III included men whose sports activities were irregular, scanty and light (e.g., occasional skiing with utilization of ski lifts), walking only one to three miles a day and engaged in physically non-strenuous occupations (e.g., mechanics, practicing physicians and factory workers).

Category IV consisted of more or less completely sedentary subjects with no sports activities and with a minimum of walking (e.g., office clerks, businessmen and some medical students during the school year, even if they had been physically more active during summer vacations).

Nine students were tested twice before and once after a six-week training period in cross country running; eleven others were tested before and after a three-month period of intensive training for the "Kake-Walk," a traditional acrobatic dance competition on the campus of the University of Vermont (Fig. 4).

Group B (those thirty-five to fifty years of age) was divided into four categories in a fashion similar to group A. There were no competitive athletes in this age group. No injections or infusions were given to these subjects.

RESULTS

GROUP A. (SEVENTEEN TO THIRTY-FOUR YEARS OF AGE)

Heart rate at rest: The average heart rates of the individual exercise categories of 266 test

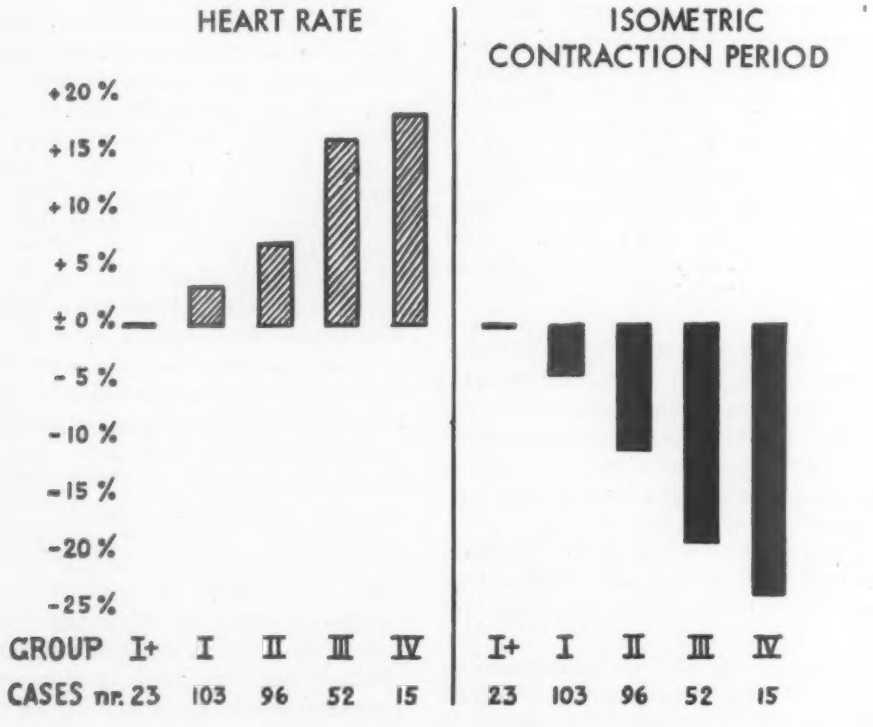

FIG. 5. Heart rate and isometric period in various exercise habit categories of group A. Maximal exercise habits in Category I+, minimal in category IV.

TABLE I

Measurements of Heart Rate and Phases of Systole in Various Exercise Categories of Group A Subjects

Group	No. Subjects	Average Age (yr.)	Average Heart Rate per Minute	Average Total Systole (TS) ($^1/_{1000}$ sec.)	Average Isometric (tension) Period (TP) ($^1/_{1000}$ sec.)	Average Isotonic (ejection) Period (EP) ($^1/_{1000}$ sec.)	Average Quotient EP:TP
I+	23	21.5	63.8	403.1	105.1	298.0	2.84
I (incl. I+)	103	22.7	66.0	394.7	100.7	294.0	2.92
II	96	22.1	68.4	382.8	93.6	289.2	3.09
III	52	24.2	74.3	368.5	85.1	283.4	3.33
IV	15	25.1	75.8	362.7	80.6	282.1	3.50

TABLE II

Measurements Before and After Six Weeks Intensive Training (Cross Country Runners)

Case No.*	Pre-training†	Before Intensive Training‡					After Six Weeks Intensive Training						
		Heart Rate	TP	EP	Q	Blood Pressure	Heart Rate	TP	EP	Q	Blood Pressure	Δ Heart Rate	Δ TP
1	0	(90)	(72)	(263)	(3.6)	(120/70)							
		(88)	(74)	(254)	(3.4)	(118/65)							
		89	73	259	3.5	119/68	64	83	277	3.3	110/50	−25	+10
2	0	(78)	(77)	(279)	(3.6)	(135/75)							
		(70)	(81)	(276)	(3.4)	(120/70)							
		74	79	278	3.5	128/72	62	86	295	3.4	112/62	−12	+ 7
3	0	(98)	(87)	(253)	(2.9)	(110/75)							
		(95)	(90)	(252)	(2.8)	(125/70)							
		96	89	253	2.9	118/73	80	104	260	2.5	110/65	−16	+15
4	+	(52)	(79)	(315)	(4.0)	(105/60)							
		(50)	(80)	(311)	(3.9)	(105/55)							
		51	80	313	4.0	105/57	54	88	310	3.5	120/60	+ 3	+ 8
5	+	(54)	(109)	(288)	(2.6)	(110/65)							
		(52)	(110)	(285)	(2.6)	(100/60)							
		53	110	287	2.6	105/62	58	101	277	2.7	110/55	+ 5	− 9
6	+	(64)	(81)	(298)	(3.9)	(115/60)							
		(64)	(84)	(282)	(3.4)	(100/60)							
		64	83	290	3.6	107/60	68	93	292	3.1	118/58	+ 4	+10
7	++	(70)	(103)	(277)	(2.7)	(120/65)							
		(68)	(105)	(276)	(2.6)	(122/65)							
		69	104	277	2.7	121/65	64	125	282	2.2	120/70	− 5	+21
8	++	(68)	(99)	(276)	(2.8)	(100/40)							
		(70)	(102)	(268)	(2.6)	(100/60)							
		69	101	272	2.7	100/50	70	94	256	2.7	100/45	+ 1	− 7
9	++	80	92	279	3.0	140/85	68	103	293	2.9	110/65	−12	+11
Average		72	90	279	3.2	116/66	65	97	282	2.9	112/59	− 7	+ 7

* The subjects were students between nineteen and twenty-two years of age.

† The degree of their respective state of training before beginning the six-week intensive training period is indicated as 0 (none), + (slightly) and ++ (well trained).

‡ The figures in parentheses represent readings obtained on two successive days.

subjects varied in reversed proportion to the degree of habitual physical exercise (Table I and Fig. 5). In fourteen of twenty temporarily (six to twelve weeks) trained subjects, the heart rate was reduced at termination of the training period (Tables II, III and Fig. 6).

Relation of heart rates to smoking habits: When each exercise habit category was subdivided into

TABLE III
Measurements Before and After Twelve Weeks Intensive Training (Kake-Walkers)

Case No.*	Pre-training†	Before Intensive Training				After Twelve Weeks Intensive Training					
		Heart Rate	TP	EP	Q	Heart Rate	TP	EP	Q	Δ Heart Rate	Δ TP
1	0	76	80	289	3.7	68	96	284	3.0	− 8	+16
2	0	72	83	263	3.2	88	103	272	2.6	+16	+20
3	+	58	88	293	3.3	54	95	303	3.2	− 4	+ 7
4	+	60	97	287	3.0	62	103	284	2.7	+ 2	+ 6
5	++	78	84	270	3.2	76	93	258	2.8	− 2	+ 9
6	++	60	74	323	4.4	57	86	307	3.6	− 3	+12
7	++	74	92	284	3.1	67	86	291	3.4	− 7	− 6
8	++	78	95	270	2.4	71	104	271	2.6	− 7	+ 9
9	++	72	97	277	2.9	62	105	273	2.6	−10	+ 8
10	++	64	91	294	3.2	52	101	303	3.0	−12	+10
11	++	62	109	298	2.7	52	111	310	2.8	−10	+ 2
Average		69	90	286	3.2	65	98	287	2.9	− 4	+ 8

* The subjects were students between nineteen and twenty-three years of age.
† The degree of their respective state of training before beginning the 12-week intensive training period for Kake-Walk is indicated as 0 (none), + (slightly) and ++ (well trained).

three subgroups (non-smokers, light smokers and heavier smokers), the average heart rates showed the same trend toward acceleration with decreasing exercise habits as the entire categories I to IV (Table IV). In other words, smoking habits did not significantly modify the apparent effect of exercise habits on the heart rate.

In addition, the percentage-wise distribution of non-smokers, light and heavier smokers, respectively, throughout the four main exercise habit categories, varied only in relatively narrow limits, although with a trend toward more smoking in the physically less active categories III and IV (Table V).

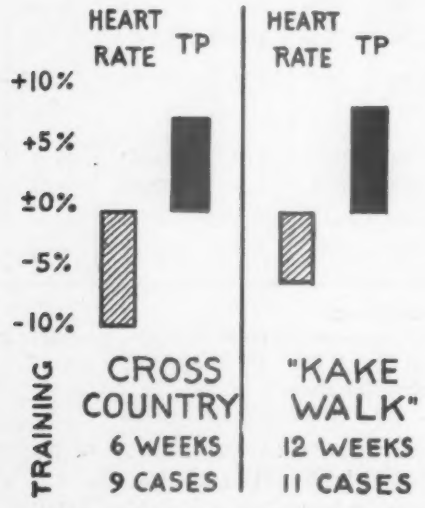

FIG. 6. Changes of heart rate and isometric period at end of temporary training periods.

Response of heart rate to atropine: An effective degree of atropinization (judged by the degree of cardiac acceleration) with the routine dose of 0.025 mg. per kg. intravenously was ascertained through the fact that seven minutes later a 50 per cent increase of this dose did not significantly further enhance the acceleratory effect of the first dose. In eight subjects, the average acceleration (41 beats per minute) was thus further increased by only 2 beats per minute.

In all atropine experiments, the physically highly active categories I and II on the one hand, and the less active plus the inactive categories III and IV on the other, were pooled for comparison. The average absolute accelerations (beats per minute) after the administration of atropine were practically identical in categories I + II as compared with III + IV. Percentage-wise (in relation to the resting heart rates), the acceleration seemed slightly more pronounced in the more active test subjects (Table VI).

Response of heart rate to infusions of epinephrine and norepinephrine (without atropine): Epinephrine accelerated the heart rate slightly less in the active pair of categories than in the less active pair. The cardiac retarding effect of norepi-

TABLE IV

Effect of Smoking Habits on Heart Rate and TP in Group A Subjects

Group	Average Heart Rate				Average TP ($^1/_{1000}$ sec.)			
	All Subjects	Non-Smokers	Light Smokers	Heavier Smokers	All Subjects	Non-Smokers	Light Smokers	Heavier Smokers
I	66.0	65.4	64.5	68.4	100.7	99.1	101.3	101.6
II	68.4	68.6	72.6	70.7	93.6	93.0	99.3	92.9
III	74.3	71.7	72.2	71.7	85.1	88.8	80.4	88.3
IV	75.8	76.3	79.0	73.0	80.6	92.0	88.0	85.0

NOTE: Persons who smoked an average of one to ten cigarettes (or approximate equivalents of cigars or pipe) a day were designated as "light smokers," those who smoked more than ten cigarettes a day as "heavier" smokers.

nephrine was practically the same in both (Table VI).

Response of heart rate to infusions of epinephrine and norepinephrine after atropine: After atropinization, the epinephrine-induced average cardiac acceleration was more exaggerated in the active pair of categories than in the less active pair (Table VI). Atropinization converted the norepinephrine-induced bradycardia into a marked acceleration which was slightly more pronounced in the pair of active categories than in the less active pair (Table VI).

TABLE V

Per Cent Distribution of Types of Smokers Throughout the Exercise Habit Groups of Age Group A

Group	Non-Smokers (%)	Light Smokers (%)	Heavier Smokers (%)
I	65	11	24
II	69	10	21
III	46	14	40
IV	57	14	29

Response of heart rate to standing before and after atropinization: The average cardiac acceleration elicited by the erect position was slightly less pronounced in the pair of active categories before the administration of atropine but more exaggerated in this pair of categories after atropinization than in the less active pair (Table VI).

Isometric period (= tension period, TP) at rest: The average length of TP of the individual exercise categories of 266 test subjects varied in direct proportion to the degree of habitual physical exercise (Table I and Fig. 5).

In seventeen of the twenty temporarily (six to twelve weeks) trained subjects, TP was slightly to markedly prolonged after termination of the training period (Tables II, III and Fig. 6).

Relation of TP to smoking habits: Like the heart rate, the length of TP and its dependence on exercise habits were not appreciably influenced by smoking habits (Table IV).

Response of TP to the administration of atropine: TP was irregularly and, as a rule, only slightly shortened by atropinization. (Increase of the routine dosage by 50 per cent did not augment the average shortening effect on TP in eight subjects: −7 versus −8 thousandths of a second.) Small differences of reaction in the pooled active pair of categories versus the less active pair were probably without significance (Table VI). However, in category I+ a shortening of TP occurred in 87 per cent of the subjects with a total average of −10.5 thousandths of a second.

Response of TP to infusions of epinephrine and norepinephrine before and after the administration of atropine: The epinephrine-induced average shortening of TP was marked and practically identical in the active and the less active pair of categories. Its accentuation by atropine was likewise practically the same in both pairs of categories (Table VI).

Norepinephrine increased the length of TP (slightly less in the more active categories). Atropine-induced conversion of this elongation to a shortening was nearly identical in both pairs of categories (Table VI).

Response of TP to standing before and after atropinization: TP was prolonged in the erect position. Accentuation of this prolongation after atropine was more pronounced in the active pair of categories than in the less active pair (Table VI).

Blood pressure and pulse pressure at rest before and

TABLE VI

Effect of Atropinization (0.025 mg./kg.) on Heart Rate and TP at Rest, During Epinephrine and Norepinephrine Infusion, and Standing (Group A Subjects)

Groups (pooled)	No. Subjects	Average Heart Rate			Average TP ($^1/_{1000}$ sec.)		
		Resting†	During Infusion (or standing)	Δ After vs. Before Atropine*	Resting	During Infusion (or standing)	Δ After vs. Before Atropine*
Resting							
I, II	165	67.4	...	↑ 38.8 (↑ 57.6%)	97.5	...	↓ 4.1 (↓ 4.2%)
III, IV	51	74.1	...	↑ 39.2 (↑ 52.9%)	84.2	...	↓ 2.9 (↓ 3.4%)
Epinephrine Infusion							
I, II	37	...	+12.9	↑ 52.3	...	−29.1	↓ 7.6
III, IV	38	...	+16.6	↑ 44.0	...	−28.4	↓ 7.4
Norepinephrine Infusion							
I, II	36	...	−11.1	↑ 61.4	...	+ 5.4	↓ 20.7
III, IV	28	...	−12.5	↑ 57.2	...	+ 7.8	↓ 21.5
Standing							
I, II	37	...	+18.0	↑ 50.0	...	+18.4	↑ 6.8
III, IV	30	...	+22.8	↑ 43.6	...	+20.0	↑ 3.3

* The arrows pointing upward or downward indicate the atropine-induced increase or decrease, respectively, of the reactions to analogous procedures before the administration of atropine.

† The percentages given in the "resting" tests after atropine are related to the respective "resting" values before atropine.

after atropinization: The average readings were nearly identical in all pairs of categories (Table VII). Atropine caused slight elevations of the average systolic and diastolic levels of a similar magnitude in both pairs of categories (Table VIII).

TABLE VII

Average Blood Pressure Values (mm. Hg)

Age Groups (yr.)	Pooled Exercise Habit Categories I, II		Pooled Exercise Habit Categories III, IV	
	Systolic	Diastolic	Systolic	Diastolic
A(17–34)	120.9	69.1	120.2	71.4
B(35–50)	124.5	75.3	121.1	75.3

Response of blood pressure and pulse pressure to infusions of epinephrine and norepinephrine before and after atropinization: Both epinephrine and norepinephrine elevated the systolic blood pressure. Epinephrine lowered, norepinephrine raised the diastolic pressure. Epinephrine increased the pulse pressure, norepinephrine left it practically uninfluenced. The averages of all these reactions were nearly identical in the active and less active pairs of categories. Atropine exaggerated the systolic pressor effects, especially that of norepinephrine. The depressant action of epinephrine on the diastolic pressure was converted to an elevation and the diastolic norepinephrine-induced rise of diastolic pressure was markedly increased after atropinization.

TABLE VIII

Effect of Atropinization (0.025 mg./kg.) on Blood Pressure and Pulse Pressure at Rest and During Epinephrine and Norepinephrine Infusion (Group A Subjects)

Groups (pooled)	No. Subjects	Average Systolic Blood Pressure			Average Diastolic Blood Pressure			Average Pulse Pressure		
		Resting	During Infusion	Δ After vs. Before Atropine	Resting	During Infusion	Δ After vs. Before Atropine	Resting	During Infusion	Δ After vs. Before Atropine
Resting										
I, II	165	120.9	...	↑ 6.0	69.1	...	↑ 12.1	52.0	...	↓ 6.3
III, IV	51	120.2	...	↑ 0.6	71.4	...	↑ 13.6	48.9	...	↓ 3.0
Epinephrine Infusion										
I, II	37	...	+12.4	↑ 13.8	...	−15.8	↑ 12.0	...	+28.2	↑ 12.6
III, IV	38	...	+14.5	↑ 16.2	...	−13.7	↑ 11.9	...	+28.2	↑ 5.4
Norepinephrine Infusion										
I, II	36	...	+13.1	↑ 52.8	...	+12.6	↑ 34.8	...	+ 0.5	↑ 18.0
III, IV	28	...	+14.6	↑ 55.1	...	+15.0	↑ 38.6	...	− 0.4	↑ 16.5

NOTE: The arrows pointing upward or downward indicate the atropine-induced increase or decrease, respectively, of the reactions to analogous procedures before the administration of atropine.

There were no significant differences in the reactions of the active and less active pairs of categories, respectively. The average changes in pulse pressure were accentuated by atropine. This occurred to the smallest degree in the epinephrine-infused less active pair of categories (Table VIII).

Response of blood pressure to standing: Because of the short duration of the standing periods, blood pressure measurements were frequently unsatisfactory, especially after the administration of atropine, and were therefore omitted from our records.

Response of stroke volume to atropine: In 88 per cent of the subjects tested, a diminution of the stroke volume occurred after the administration of atropine. The total average was −22.3 per cent according to the method of Wezler-Böger and −16.7 per cent according to the method of Broemser-Ranke.

GROUP B. (THIRTY-FIVE TO FIFTY YEARS OF AGE)

Heart rate at rest: As in group A, the average heart rates increased with declining exercise habits (Table IX and Fig. 7). The span

TABLE IX

Measurements in Group B Subjects

Group	No. Subjects	Average Age (yr.)	Average Heart Rate (per min.)	Average Total Systole (TS) ($^1/_{1000}$ sec.)	Average Isometric (tension) Period (TP) ($^1/_{1000}$ sec.)	Average Isotonic (ejection) Period (RP) ($^1/_{1000}$ sec.)	Average Quotient EP:TP
I	17	40.5	59.9	404.9	112.9	292.0	2.66
II	31	41.4	67.4	384.2	103.8	280.4	2.70
III	22	41.2	72.9	376.0	98.5	277.5	2.82
IV	24	42.0	74.5	372.3	93.2	279.1	2.99

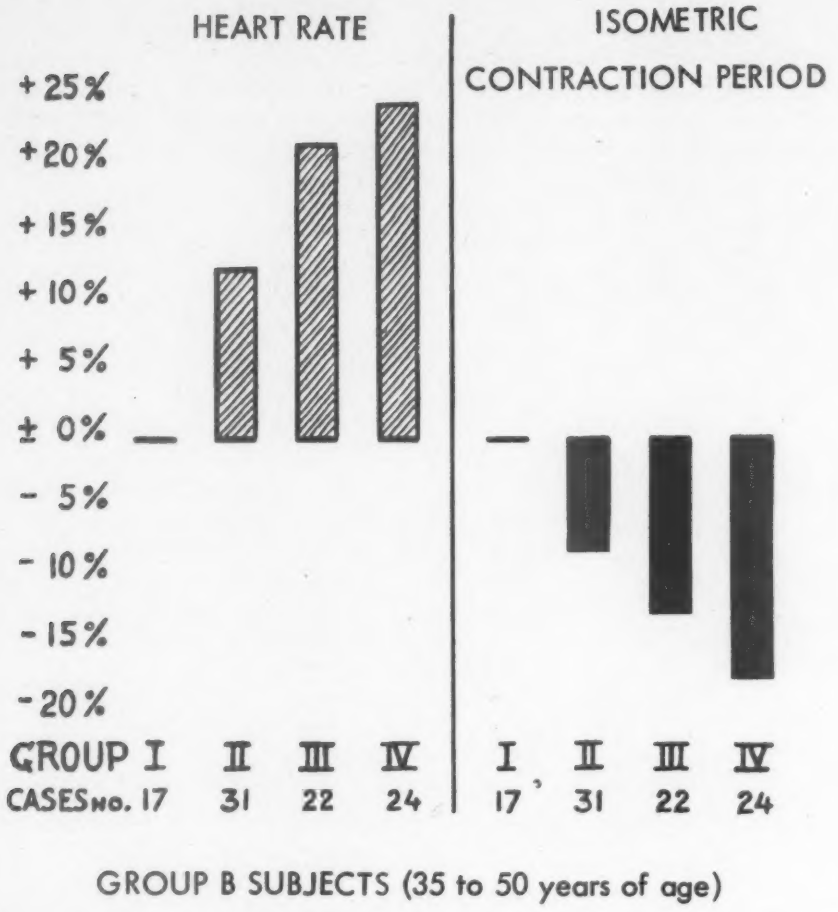

FIG. 7. Heart rate and isometric period in various exercise habit categories of group B. Maximal exercise habits in category I, minimal in category IV.

between the averages of exercise habit categories I and IV was somewhat larger (14.6 beats per minute) than in the younger subjects (9.8 beats per minute).

Isometric period at rest: As in group A, the average TP decreased with declining exercise habits. All TP averages in this age group were approximately 12 thousandths of a second longer than in the corresponding categories of the younger subjects (Table IX).

Smoking habits: As in group A, smoking habits did not appreciably affect the trend of the heart rate to increase, and of the TP to become shorter with decreasing exercise habits (Table X). Only the values of the light smokers (less than ten cigarettes or equivalent per day) were

TABLE X

Effect of Smoking Habits in Group B Subjects

Group	Average Heart Rate				Average TP ($^1/_{1000}$ sec.)			
	All Subjects	Non-Smokers	Light Smokers	Heavier Smokers	All Subjects	Non-Smokers	Light Smokers	Heavier Smokers
I	59.5	59.7	58.0	61.7	112.9	110.4	120.0	112.3
II	67.4	66.2	66.3	68.9	103.8	108.5	97.3	100.4
III	72.9	72.7	80.0	71.4	98.5	98.7	94.0	97.3
IV	74.5	74.1	60.0	74.2	93.2	93.4	101.0	87.5

TABLE XI
Per Cent Distribution of Types of Smokers in Group B

Group	Non-Smokers (%)	Light Smokers (%)	Heavier Smokers (%)
I	60	20	20
II	46	22	32
III	33	17	50
IV	70	4	26

somewhat irregular, due to the small number (Table XI), in which individual variations affected the averages more conspicuously.

Comments

The salient feature of our test results on a total of 360 men (aged seventeen to fifty) with graded exercise habits was a linear increase of the heart rate and a linear decrease in length of the isometric period (TP) of the left ventricular dynamic cycle with decreasing degrees of habitual physical exercise.

Even though a large body of literature has been devoted to the cardiac manifestations of "athlete's heart" as representing abnormal if not pathological "plus deviations" from the "normal" majority pattern of contemporary Western populations, we prefer to place the main emphasis on the prevailing "minus deviations" of the latter. Hypothetically compared with better conditioned generations of the past and with primitive tribes of our time, in which the impact of civilization has not yet worn down the original bodily characteristics of the species *homo sapiens*, the present-day athletic minority of the civilized West represents the biologically, if not numerically, more "normal" type. It will, therefore, be used as the basis of our quantitative comparisons.

In a sense, the expansion of our studies from Vermont to the Austrian Alps constituted an attempted semi-epidemiological approach to the problem of exercise habits and neurovegetative cardiac regulation, insofar as the Medical Clinic in Innsbruck offered an easier access to a relatively large number of habitually vigorously exercising test subjects than our Cardiovascular Research Unit in Burlington. The distribution of American and Austrian test subjects, respectively, throughout the four exercise habit categories is shown in Table XII. Obviously, this does not, by any means, represent epidemiologically valid cross sections of these populations but may well be considered as roughly indicative of general exercise trends in two comparable provincial urban centers with mountainous farmland surroundings.

Heart Rate at Rest

The well known slow heart rate of highly trained endurance athletes (e.g., 36 beats per minute, according to a personal communication received from an Australian Marathon runner) has been suspected by some as indicating a primary constitutional trait that predisposes to athletic inclinations and abilities, rather than being secondarily induced by systematic exercise habits. This opinion is largely contradicted by the following observations:

(1) A progressive reduction of the heart rate takes place during training periods of only a few weeks or months, as observed by others[33,36,65–68] and by ourselves (Tables II, III and Fig. 6). Higher initial heart rates seem to display a more marked tendency to be depressed by training than lower ones.[65,66] In

TABLE XII
Percentage-wise Distribution of Exercise Habit Categories Among American and Austrian Test Subjects

Age Groups	Location	I (%)	II (%)	III (%)	IV (%)	No. Subjects
17–34	Burlington	3	54	31	12	125
	Innsbruck	70	21	9	0	141
35–50	Burlington	2	23	33	42	57
	Innsbruck	43	49	8	0	37
17–50	Burlington	3	44	32	21	182
	Innsbruck	65	26	9	0	178

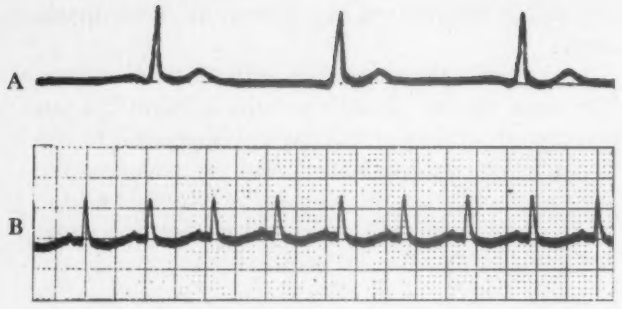

FIG. 8. A, electrocardiogram of Professor Arnold D., aged eighty-seven, unusually heavy exercise habits. B, electrocardiogram of Miss B. C., aged sixty-nine, extreme physical inertia.

our temporarily (six to twelve weeks) exercised subjects, the average reduction of rates above 70 beats per minute (average 79) was −7.3 beats, that of rates below 70 (average 61) was only −1.9 beats. Among older ex-champions (average age 44.4 years), Cureton[30] noticed the highest persisting vagal tone (or sympathetic inhibition?) in those who kept up an intensive training program. Otherwise, the antiadrenergic gains of systematic exercise are usually lost after cessation of training.[33]

(2) As a counterpart to the training-induced bradycardia, Taylor et al.[69] have observed the opposite, namely, marked cardiac acceleration in healthy subjects after three weeks of voluntary bedrest, with a slow (two to three weeks) return to normal.

The two following examples may illustrate the apparent influence on the heart rate of unusually persistent exercise habits on the one hand, and of extreme physical inertia on the other:

Professor Arnold D., an eminent scientist and noted Alpinist, former head of the Department of Physiology at the University of Vienna (eighty-seven years old) has lived alone for the past twenty years with his paralyzed wife and a library of several thousand volumes in a 15th century isolated log cabin above Schruns, Vorarlberg, at an altitude of 5,000 feet. He cuts trees for his firewood, raises his own vegetables, does all household chores, digs a path through deep snow on a precipitous slope, fetches mail and groceries twice weekly from a village in the valley and carries them up one and one-half hours to his abode. He makes extensive climbing or ski excursions alone to high peaks (up to eighteen hours in a stretch) nearly every weekend; he does daily calisthenics at home. He still follows the scientific literature, writes articles and lectures occasionally. In recent years he had a few episodes of auricular fibrillation but no signs of cardiac failure. His heart rate at rest is 48 to 60, at arrival on mountain peaks about 90 (Fig. 8A).

Miss B. C., a sixty-nine year old spinster; former piano teacher; decided at the age of thirty-seven, when her father died, to spend her life in bed. She stayed in bed for thirty years without interruption (except for one walk around the house after two years), wrote a large book about the courtship of her father, numerous poems and musical compositions. At the age of sixty-seven, when her older sister and housekeeper died, she learned again slowly to walk and now spends a few hours out of bed every day. She does not do any housework. She has a small palpable thyroid nodule but there are no signs of thyrotoxicosis. Her protein-bound iodine is low. Her heart rate, which had been over 100 for many years, is now up to 140 despite digitalization (Fig. 8B).

ISOMETRIC (TENSION) PERIOD (TP) OF THE LEFT VENTRICLE AT REST

The length of the isometric period of the left ventricle serves as a useful criterion of adrenergic positive inotropic, and sympatho-inhibitory-cholinergic (?) negative inotropic influences, respectively, on cardiac dynamics, in relative quantitative and causal independence of heart rate and peripheral resistance. In the normal heart, the only major interfering factors are alterations of ventricular filling.[40,55,70,71] This accounts for the often marked prolongation of TP in the erect position.[55] We have confirmed this phenomenon (Table VI and Fig. 1) which, during standing, usually overcompensates for the effects of reflexly increased sympathetic activity and catecholamine discharges[39,72] on the TP.

The results obtained with Blumberger's bloodless graphic method of measuring the isometric period of the left ventricle[40] are in close agreement with those obtained by direct needle puncture of the ventricle[73] and by retrograde catheterization of the aorta.[74] Repetitions on successive days (Table II) showed them to be reproducible with sufficient accuracy.

A characteristic prolongation of TP, due to an augmented vagal and/or decreased sympathetic tone, has been described in athletes by Klepzig,[51a] Emmrich et al.[55] and Mellerowicz.[33] However, no attempts have been made previously to grade the TP changes according to exercise habits at lower levels of activity (Tables I, IX and Figs. 5 and 7), and to interpret the opposite, adrenergic preponderance-induced TP shortening as a characteristic feature, resulting from lack of exercise.

In both age groups (seventeen to thirty-four and thirty-five to fifty years), respectively, this

progressive deficiency of sympatho-inhibitory or cholinergic inotropic mechanisms and corresponding augmentation of adrenergic preponderance in proportion to declining exercise habits was demonstrable as a corollary to the deficiency of cholinergic or sympatho-inhibitory chronotropic mechanisms manifested by progressive cardiac acceleration. A significantly longer average TP and a slightly slower average heart rate in all exercise habit categories of the older age group, compared with the younger one, suggested a generally higher degree of cardiac sympathetic inhibition or vagal tone as prevailing between the thirty-fifth and fiftieth year.

After termination of relatively short but vigorous training periods, we found a shift away from the adrenergic side both concerning the heart rate and TP (Tables II, III and Fig. 6). The average prolongation of isometric periods shorter than 90 thousandths of a second (average 81.3) was +11.4 points, that of isometric periods longer than 90 (average 98.8) was only +4.5 points. Thus, the training-induced shift of both the heart rate and the TP away from the adrenergic side appeared generally more pronounced in those subjects whose sympathetic tone had been relatively high before training was begun.

In the patient whose heart rate ranged between 100 and 140 after thirty years' bedrest, TP was on two occasions 63 and 68 thousandths of a second, respectively, thus below the lowest value (74) of our older age group. This seemed indicative of a maximal degree of sympathetic preponderance resulting from an extraordinary lack of exercise.

BLOOD PRESSURE AT REST

The behavior of the resting blood pressure in relation tc exercise habits is much less characteristic than that of the heart.[65] In our series there was no major difference between the pooled active (I, II) and less active (III, IV) categories of both age groups concerning either the average systolic or diastolic pressure (Table VII). Other observers[17,33,36] have noticed in trained subjects a slight lowering of the systolic and elevation of the diastolic pressure, suggesting a diminution of the cardiac stroke volume.

EPINEPHRINE AND NOREPINEPHRINE INFUSIONS; STANDING

The generally cardioacceleratory and TP-shortening influence of infused and secreted epinephrine and the opposite effects of infused norepinephrine have been discussed by us elsewhere.[39,75]

A slightly more intense cardiac acceleration during the infusion of epinephrine and during standing in the pooled less active categories III, IV (Table VI) seems consistent with a less potent cholinergic or sympatho-inhibitory counterregulatory effectiveness in these subjects. Category differences of TP reaction to epinephrine infusion and standing were insignificant.

It is noteworthy that the specific cardiac adrenergic properties of norepinephrine are entirely obscured by powerful vagal (and/or sympatho-inhibitory?) counterregulatory reflexes which are elicited by the injection or infusion of norepinephrine due to its action on the peripheral pressoreceptors (cardiac retardation, prolonged TP) (Fig. 1 and Table VI). The average heart rate reactions of the exercise habit categories to the infusion of norepinephrine were not significantly different. The reflectory TP prolongation appeared slightly exaggerated in the less active categories. No explanation for this can be offered.

EFFECTS OF ATROPINIZATION

The fact that atropine was found to cause a slight diminution of the blood catecholamines,[76] has probably no bearing on the cardiac reactions. Kauf[77] observed in sportsmen a near ineffectiveness (concerning heart rate) of 1 mg. atropine sulfate, subcutaneously applied, and ascribed this to a high vagal tone which would require a larger dosage to be extinguished. Accordingly, the double dose caused regularly cardiac acceleration.

In our series, there was a certain discrepancy between the marked, and without exception accelerating, effect of atropine on the heart rate, on the one hand, and the rather irregular shortening of TP on the other. The latter occurred in only 62.5 per cent of all subjects. This discrepancy may be explained, in part, by interference of the stroke volume-diminishing and thus, conceivably, TP-lengthening hemodynamic effect of atropinization. Furthermore, it is possible that atropine, while blocking the vagal effects at the sinus and atrioventricular nodes, and thus causing regularly cardiac acceleration, does not act directly on the non-neurogenic autochthonous acetylcholine stores of the ventricles[24] which have no vagal nervous supply. Accordingly, the neurovegetative modifications of the length of TP may depend more on the

equilibrium between sympathetic excitatory and inhibitory central influences, respectively, than on that between sympathetic and vagal impulse formation.

Cardiac acceleration after atropinization was percentage-wise slightly less pronounced in the less active categories III, IV. The shortening of TP did not show a significant difference between the paired categories I, II versus III, IV, but it was quite regularly present in the subcategory I+ with maximal readings (−41 and −31 thousandths of a second, respectively) in a long-distance runner and a long-distance skier.

The quantitative differences between the chronotropic and inotropic changes after atropinization make it difficult to evaluate the preexisting vagal tone on the basis of the reactions to atropine. This likewise applies to the comparison of reactions to infusions of epinephrine and norepinephrine and to standing before and after atropinization (Table VI). Nevertheless, in general, the impression prevails that in the physically less active categories of subjects the elimination of counterregulatory vagal tone by atropine caused a less pronounced shift toward adrenergic preponderance than in the highly active categories. In other words, the former categories appeared to be endowed with less potent cardiac antiadrenergic mechanisms than the latter. This interpretation is in keeping with the concept of a cardiac cholinergic and/or sympatho-inhibitory deficiency, as manifested by a high resting heart rate and a short TP in the low exercise groups.

The behavior of the blood pressure without and with atropine (Tables VII and VIII) in the physically active and inactive categories did not reveal any differences significant enough to suggest a major influence of physical exercise habits on the vascular neurovegetative status.

The less pronounced accentuation of epinephrine- and norepinephrine-induced pulse pressure increases after atropinization in the less active categories III, IV may be attributed to a presumably weaker effect of atropinization on the cardiac stroke volume in these categories.

FACTORS DETERMINING CARDIAC NEUROVEGETATIVE EQUILIBRIUM

The fact that lack of exercise leads to an augmentation of cardiac sympathetic and regression of cardiac vagal and/or sympatho-inhibitory activity, and that prolonged exercise acts in the opposite direction, makes it mandatory to search for factors responsible for this phenomenon.

The cardiac manifestations accompanying exercise are largely of centrogenic origin,[78] mediated by discharges of norepinephrine directly into the heart muscle and by the mobilization of catecholamines from the adrenal medulla.[23,24,79–84] The heart muscle avidly absorbs and stores catecholamines from the circulating blood[85–87] and, likewise, accumulates norepinephrine, discharged from stimulated cardiac sympathetic nerves.[85] Thus it appears possible that exercise-induced and frequently repeated influxes of catecholamines into the myocardium gradually alter either the local enzymatic situation (decreased cholinesterase?, increased cholinacetylase?) or the myocardial cellular responsiveness to vagal and autochthonous ventricular acetylcholine. Danielopolu's old hypothesis[88] which postulates an equilibrated mutual release of catecholamines and acetylcholine in the myocardium seems to be gaining support from newer observations; locally formed catecholamines (especially norepinephrine)[89–91] are liberated from the myocardium by acetylcholine, and acetylcholine is released from the electrically driven heart.[91,92] However, a liberation of cardiac acetylcholine, possibly from the ventricular "proacetylcholine" stores[93] by local catecholamine action remains yet to be demonstrated.

The observation that in treadmill-trained dogs the mere sight of the treadmill evokes the cardiac manifestations, otherwise elicited by exercise itself,[78] suggests that the cardiac neurovegetative reactions to both optimal and excessive training may have their ultimate roots in shifting stimulus formations within the central nervous system.[127] As far as the latter is concerned, it should be kept in mind that sympathetic inhibitory and vagal stimulatory centers are concentrated in closely adjacent cerebral areas,[129] whereas the central representation of sympathetic stimulation occupies more caudal sections between the level of the inferior mamillary bodies and C7.[133]

The phenomenon of "overtraining," consisting of an exaggerated cardiac adrenergic tone, and potentially resulting in damage to the heart muscle,[17,94–97] may be ascribed to an excessively prolonged local catecholamine activity in the myocardium.

EFFECTS OF SMOKING HABITS

Despite the acutely stimulating action of nicotine on the sympathetic ganglia and the adrenal

medulla,[98] and despite the usual immediate cardioacceleratory and TP-shortening effects of tobacco smoking,[99] habitual smoking, surprisingly, did not seem either to accentuate the development of lasting cardiac adrenergic preponderance in inactive subjects or to interfere with the building up of a potent basic sympathetic inhibition or vagal tone in active ones. This may be explained both by the "amphotropic" influence of nicotine on vagal as well as sympathetic ganglia, and by the relatively evanescent (within about thirty minutes) stimulating effect of smoking one cigarette on the cardiac sympathetic tone.[99]

CLINICAL IMPLICATIONS

The clinical implications of an inactivity-induced preponderance of potentially oxygen-wasting, hypoxia-producing and efficiency-impairing adrenergic catecholamine action on the heart muscle are manifold. As pointed out elsewhere,[23,24] an exaggerated acute or chronic cardiac catecholamine activity, either due to excess formation and accumulation of catecholamines or due to inadequate cholinergic and/or sympatho-inhibitory counterregulation, may be assumed to play a prominent and often decisive role in the origin of pathological conditions, such as angina pectoris, certain arrhythmias, acute and chronic congestive heart failure, myocardial biochemical necrotization and "physiological" cardiac death.

Evidently, the danger of an occurrence of severe catecholamine-induced functional and structural derangements of the heart will be greatly augmented in the presence of coronary sclerosis which reduces the oxygen supply, and of arterial hypertension with or without cardiac hypertrophy which increases the oxygen requirement of the heart muscle. Presumable participation of catecholamine overactivity in the early predisposing stages of atherosclerosis[27,100] may add another ominous aspect to the cardiac hazards resulting from inactivity-induced adrenergic preponderance.

Former beliefs, according to which prolonged strenuous physical exercise, even in young, healthy subjects, was dangerous for the heart, have been amply refuted in more recent years.[12,14,17,30,31,67,68,101,102] Extensive statistics of Morris,[7] Luongo,[10] Pomeroy and White,[12] Karvonen et al.,[14a] Spain and Bradess[14c] and the Vienna Communal Insurance Organization[13] are strongly suggestive of a significantly lower degenerative cardiac morbidity and mortality in occupational groups with a higher degree of physical activity, and of augmented longevity in persons who maintain a fair measure of exercise habits until their later years.

According to recent observations of Morris and Crawford,[103] the injurious influence of lack of physical exercise manifests itself far more impressively in the structural condition of the heart muscle (focal myocardial fibrosis) than in that of the coronary vessels (atheromatosis). In a population with a high fat consumption, the occurrence of coronary atheromatosis was found rather evenly distributed among the occupational groups, whereas myocardial fibrosis, a typical sequel of excessive local catecholamine action, predominated strikingly in the under-exercised groups. Thus, it appears that habitual exercise, although diminishing myocardial metabolic and structural vulnerability, does not contribute much to the protection of the coronary arteries against atherosclerosis.

Evidently, to attribute cardiac degenerative diseases and deaths to lack of exercise alone would be equally as arbitrary and unwarranted as it is to attribute them to nutritional or emotional and social factors alone, no matter how important the latter may be as contributory elements.[2,5,6,104,105] The problem is too complex to be solved by one single simple formula.

In man, exercise habits do not exert any significant influence on serum cholesterol levels.[21] However, the pathogenic potentialities of a high fat and cholesterol intake seem to be aggravated by a coincidence with adrenergic overaction on the blood vessels, due to the injurious influence of the latter on the arterial intima[106,107,134] and to the predisposition for an intimal accumulation of lipids which it creates.[97,100,108,109] This last-named factor may largely account for the apparently accelerated and intensified development of coronary sclerosis and of its myocardial sequelae under the influence of adrenergic bombardments of the vascular system by tobacco smoking[110] and by prolonged socioeconomic emotional pressures, stresses and responsibilities.[104,105]

The failure of Stamler,[111] Russek,[104] and Friedman and Rosenman[105] to ascertain a definite influence of exercise habits on cardiac morbidity among city dwellers with a presumably fat-rich diet, selected and grouped primarily according to social and emotional characteristics as the dominant feature, illustrates the difficulties that stand in the way of attempts to separate overlapping and mutually aggravating factors

regarding their individual pathogenic significance.

A deeper insight into the neurovegetative cardiac aspects of exercise habit patterns in connection with their psychic motivations will undoubtedly permit a more systematic and more rational development of already existing trends toward the prophylactic as well as curative utilization of physical exercise: medically supervised reconditioning of quietly degenerating, even though still seemingly healthy, middle-aged sedentary candidates for cardiovascular disease,[31,67,68,113–118] and cautious but persistent rehabilitation of overt cardiac patients.[113,114,119–126,128] At the Sports Medical Congress in Moscow in June 1958, not less than nineteen papers on cardiac reconditioning and rehabilitation by systematic physical training were presented by speakers from all over the Soviet Union. This large material of clinical observations and the strong theoretical emphasis of Pavlovian Medicine on neural pathogenic mechanisms should provide a valuable cornerstone for future international research programs in the field of cardiovascular epidemiology.

Summary

The influence of habitual vigorous exercise and of the lack of it, respectively, on the basic cardiac neurovegetative status at rest was studied in 360 healthy American and Austrian men (seventeen to fifty years of age), ranging from competitive athletes, mountaineers and Alpine soldiers to completely sedentary persons.

Heart rate and the dynamic cardiac cycle (chronodynogram) at rest with special consideration of the isometric period of the left ventricle (total systole minus ejection period) were used as criteria of cholinergic, sympatho-inhibitory and adrenergic chronotropic and inotropic influences, respectively. In 216 subjects, the effects of vagal elimination (atropinization), in seventy-five the effects of infused epinephrine, and in sixty-four of norepinephrine, before and after atropinization, were recorded.

The results, especially the basic resting values, reveal a linear increase of cardiac sympathetic tone and decline of cardiac neurovegetative counterregulatory effectiveness in proportion to decreasing degrees of habitual exercise. Physical training periods reversed the situation.

Smoking habits (ranging from non-smoking to heavy smoking) seemed to leave the basic cardiac neurovegetative status unaltered despite the immediate adrenergic cardiac effects of tobacco smoking.

The cardiovascular metabolic and functional hazards of physical inactivity-induced potentially oxygen-wasting, cardiac efficiency-impairing, myocardium-damaging and possibly atherogenesis-promoting adrenergic overactivity are discussed.

Expanded epidemiological studies of primary neurovegetative factors together with other correlated pathogenic conditions (dietary, social, emotional), and the development of medically supervised, prophylactic mass reconditioning programs for degenerating sedentary populations are being urged.

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An Index for the Measurement of the Degree of Aortic Incompetence*

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THE PRINCIPLE underlying the technic here considered is to employ a pneumatic cuff which, when placed around the arm and inflated to certain pressures, has a valve-like action upon the brachial artery. This valve-like action had been noted in earlier observations.[1–3]

It was considered of value to see whether or not such a valve-like cuff, when applied to the brachial artery in aortic incompetence, would prevent regurgitation. The measurement of the increase in forward flow that would occur in the brachial artery as a result of the application of such a pressure cuff would provide a measurement of the amount of blood that was previously regurgitating in the brachial artery, and by this means it might be possible to provide an index for the measurement of aortic regurgitation.

MATERIAL AND METHOD

A light, plastic forearm-hand plethysmograph was employed. It was connected to a float chamber which recorded with a frontal writing point.

An important feature of the procedure was the recording of the "blood flow" with the arm in the upward and vertical position (10 to 15 degrees from the vertical). The plethysmograph was supported by an elastic band in order to counterbalance its weight and was rendered mobile by a small undercarriage with wheels which rolled on a smooth slanting board.

Thus, with the limb in an upward position, the plethysmograph was "weightless" and moved in a sufficiently free manner that artifacts did not occur due to the movements of the limb in or out of the plethysmograph. The pressure cuff was a sphygmomanometer cuff specially designed for children by Mr. B. M. Hanafin of Baum & Co., Copiague, New York. It was made of an indistensible, light plastic material on the external surface, while the inner surface applied to the arm was distensible. A layer of adhesive plastic, which prevented slipping of the cuff when the pressure was applied, lay between the layers of the cuff.

The blood flow was recorded by venous occlusion plethysmography and the results are expressed as cubic centimeters of volume change per 100 cc. of limb volume per minute.

RESULTS

NORMAL SUBJECTS

An examination was made of the influence of various cuff pressures upon the blood flow of the forearm and hand when it was held in both the *horizontal* and *vertical* positions. Figure 1 illustrates the results obtained in normal subjects.

When the arm is in the *horizontal* position it will be observed that once the venous occluding pressure is adequate (in this case 20 mm. Hg), the recorded blood flow is not significantly different from that at higher cuff pressures, but forms a plateau until the diastolic pressure is reached. Further increases of cuff pressure will cause a progressive decline in blood flow until the systolic value is reached, at which point no further change in volume is recorded.

Examination of the blood flow records in the same normal subject on the same occasion when the arm is held in the *vertical* position shows certain differences. First, the flows are much less, approximately 2 cc./100 cc./minute in the vertical position, as compared with 6.5 cc./100 cc./minute in the horizontal position. Second, it will be noted that when the arm is in the vertical position a higher cuff pressure is required to reach a plateau of blood flow measurement. In this case it was 40 mm. Hg, as compared with 20 mm. Hg when the limb was in the horizontal position. Also, the plateau ends and the measurements fall off at a lower pressure in the vertical than in the horizontal position.

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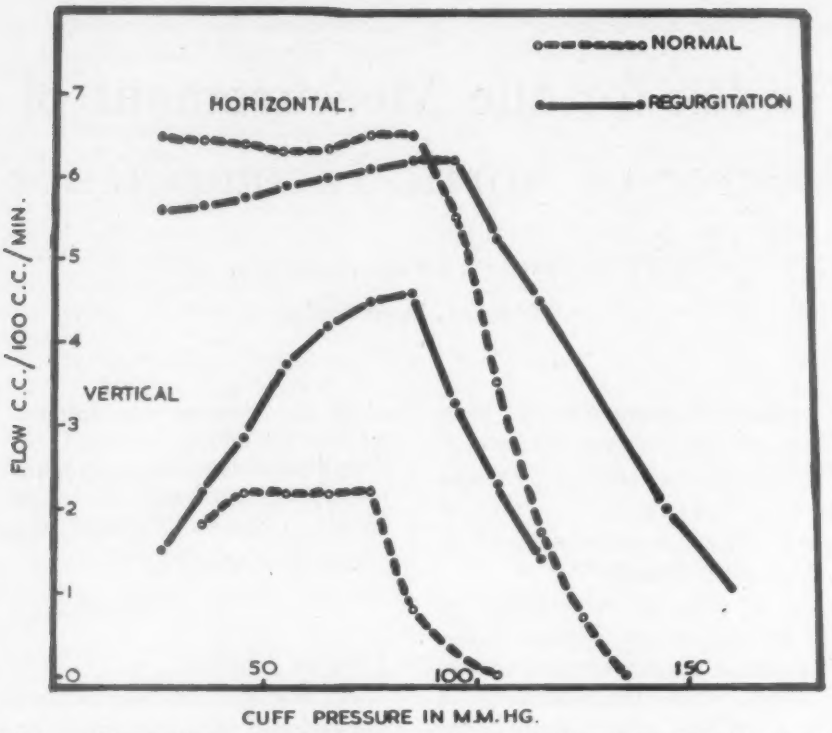

FIG. 1. Comparison of the influence of various cuff pressures on the blood flow in the forearm and hand of a normal subject and a patient with aortic regurgitation. Two positions were adopted, that of the upward, 10 to 15° from the vertical, and the horizontal. Blood flow is recorded in cc./100 cc./minute, and the cuff pressures in mm. Hg. The points on the curves are plotted from the averages of a series of experiments. Ambient temperatures were 30° to 32°C.

When blood flow records are made with the arm in the horizontal position, there is a sudden increase in limb volume immediately after the application of the occluding pressure in the cuff. This is not, however, the case when the arm is in the vertical position, for a short period of five to fifteen seconds may elapse, depending on the distance of the cuff from the plethysmograph, in order to allow the veins between the cuff and the plethysmograph to fill. Following this the limb volume will increase, at first gradually, and then more rapidly to a maximum rate of increase, and finally will tail off to a plateau (see upper curve, Fig. 2). In all blood flow measurements recorded with the limb in the vertical position, the maximum rate of increase of limb volume was measured, and not the initial increase of limb volume. When the limb was in the horizontal position the blood flow was calculated from the initial increase of limb volume (which is the maximum in this position).

PATIENTS WITH AORTIC INCOMPETENCE

In a patient with aortic incompetence (Fig. 1), with the limb in the horizontal position, the results recorded in this instance are similar to those of a normal subject. It will be observed that there is a small and progressive increase in rate of flow as the cuff pressures increase up to the point where compression of the artery takes place. In some subjects this increase with increasing cuff pressures is very marked in the horizontal position.

With the arm in the *vertical* position, the behaviour of blood flow in aortic incompetence in relation to occluding pressures is different in that there are marked increases in blood flow as higher cuff pressures are applied. Examination of the lower curves in Figure 1 demonstrates this difference.

Figure 2 shows three tracings of volume records of the forearm and hand made by venous occlusion plethysmography on a patient with aortic regurgitation, with the limb in the vertical position. The figures on the left represent the cuff pressures applied, and the figures over the tracings are the calculated blood flow values. The patient had a blood pressure of 200/25 mm. Hg. (All blood pressure figures are those

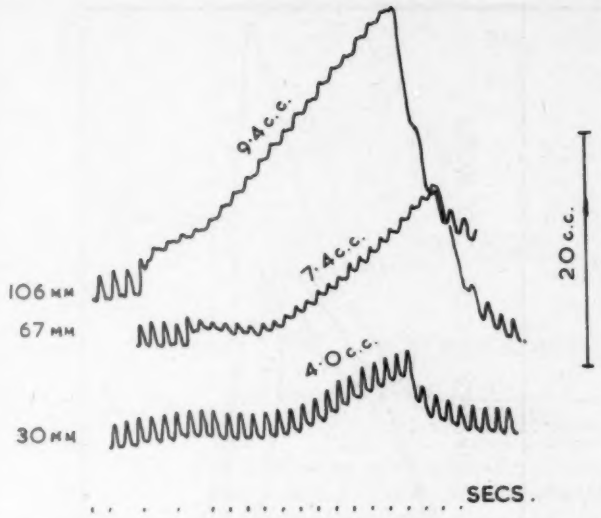

FIG. 2. Three tracings of volume records made by venous occlusion plethysmography from the forearm and hand of a patient with aortic regurgitation (blood pressure 200/25 mm. Hg). The arm was held in the upward and near vertical position. The figures on the left represent the cuff pressures in mm. Hg, the figures over each tracing, the flow rate in cc./100 cc./minute.

recorded by the auscultatory method.) These volume records made from the plethysmograph are inadequate for the purpose of examining pulse waves, but they help to explain the phenomenon that is responsible for the results seen in Figure 1. A comparison of these three curves shows that at the lower cuff pressure of 30 mm. Hg there is a marked rise and fall in pulsation. This becomes less at 67 mm. Hg, and at 106 mm. Hg the pulsations have taken on a step-like character. The higher the cuff pressure, the greater the rate of increase of limb volume. Thus, from 30 mm. Hg cuff pressure to 106 mm. Hg there is an increase in blood flow from 4 cc. to 9.4 cc./100 cc./minute.

The appearance of the curves suggests that the cuff is acting in a valve-like manner, albeit not as a perfect valve. A cuff pressure of 106 mm. Hg causes a reduction in the amplitude of the anacrotic limb, suggesting that it is causing some obstruction, but closer examination of the character of the pulse shows that it changes to that of a dicrotic nature. This is not clearly indicated in Figure 2, but can be seen by examining optical recordings made from the plethysmograph.

It can thus be seen that in aortic incompetence application of increasing cuff pressures, with the limb in the upward vertical position, may cause a marked increase in the forward flow in the arm. This is different from that of the

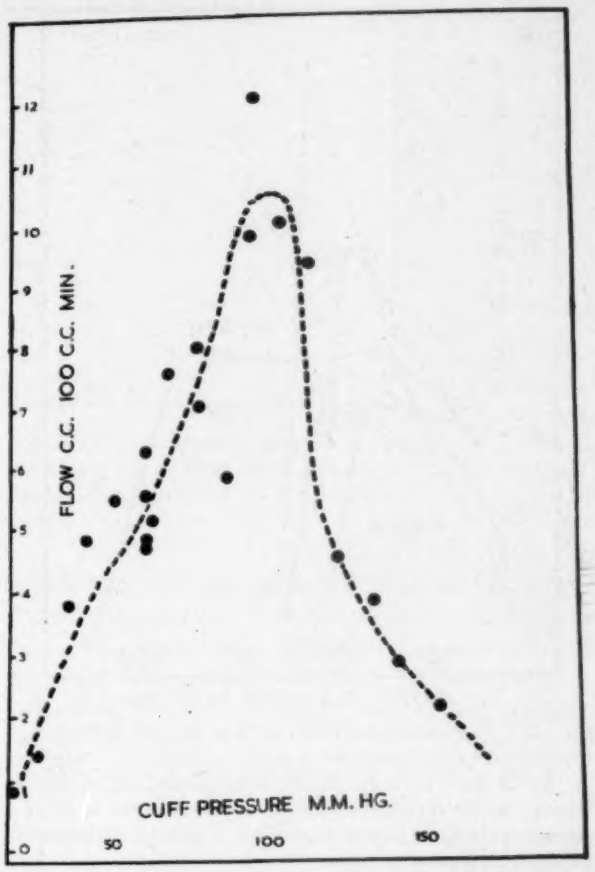

FIG. 3. Graph of a single experiment on a patient with aortic regurgitation (blood pressure 180/30 mm. Hg). It is constructed by drawing the line through the mean of the individual measurements shown as points.

normal subject and it is suggested that this increase in forward flow represents blood that was previously flowing backward from the limb, and therefore, indirectly, may provide an indication of the degree of regurgitation in the limb circulation.

Technical Precautions: There are two important features that should be noted concerning the technic: first, the placing of the limb in the upward position, and second, the use of a high ambient temperature (30 to 32°C. was used in these tropically acclimatised subjects) to induce vasodilatation.

The following precautions were observed in the technic: (1) rest between measurements; (2) time for maximum limb drainage before making a record;[4] (3) at intervals throughout the experiment, cuff pressures set at a value between 60 to 70 mm. Hg were applied in order to observe whether there were any changes in vascular tone occurring during the course of the experiment. These records were used to draw a baseline from which the final graph was

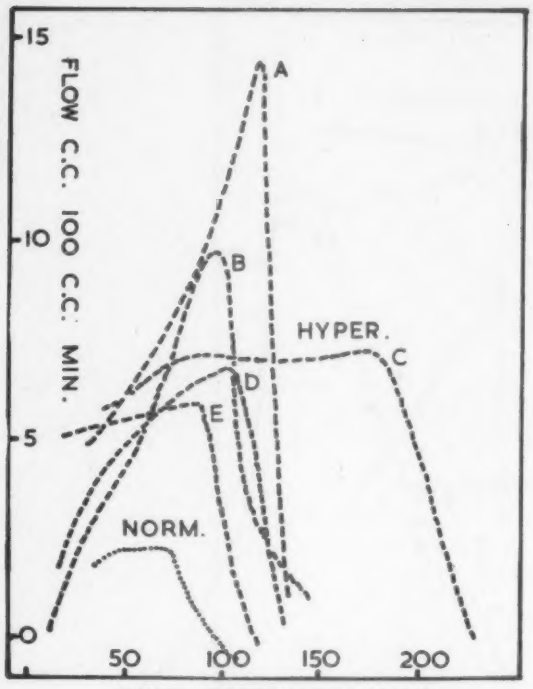

FIG. 4. Curves relating blood flow to cuff pressure in individual experiments on a series of subjects. Subjects A, B, D and E were patients diagnosed clinically as having aortic regurgitation. The lower curve is from a normal subject. Curve C is from a patient with hypertension, as shown in Figure 7.

constructed;[5] and (4) the order in which the pressures were applied was alternated in successive experiments.

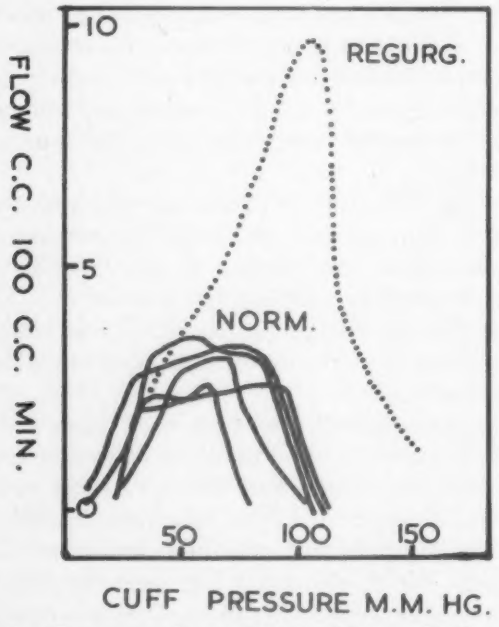

FIG. 5. Five curves from normal subjects. Each curve represents the average of a series of experiments. For comparison the curve from a single experiment on a subject with aortic regurgitation is superimposed.

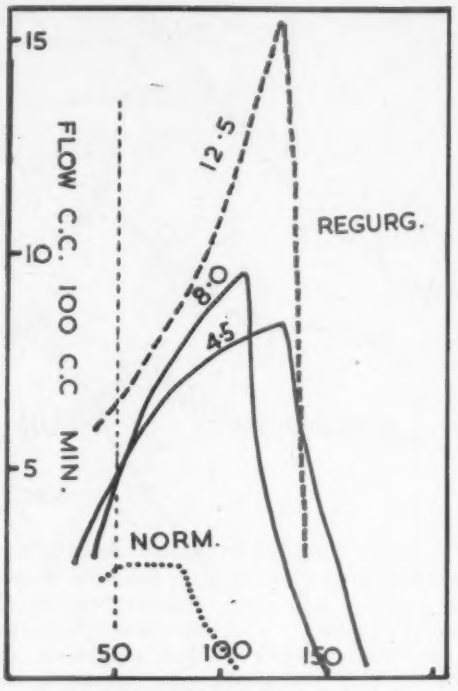

FIG. 6. Three graphs from single experiments on the same patient with aortic regurgitation. The upper dotted line was recorded while the patient was sweating profusely. The lower curve from a normal subject is superimposed for comparison.

Representative Curves: Blood flow records under ideal conditions are variable, so it is not surprising that under the conditions employed here, with the limb in the upward vertical position and with high ambient temperatures of 30 to 32°C. in a patient with aortic incompetence, the scatter of measurements should appear as seen in Figure 3. The graphs were constructed by a line through the mean of the points. Figure 4 shows curves from different subjects. The curves labelled A, B, D and E were from four patients who were diagnosed clinically as having aortic regurgitation. The lower curve is from a normal subject, while curve C is from a patient with hypertension.

Figure 5 presents a series of curves from normal subjects. Each curve is the average of a series of experiments, and, for comparison, one curve of a single experiment from a subject with aortic regurgitation is shown.

In Figure 6 three records from the same subject with aortic regurgitation are presented. The upper dotted curve was recorded when the ambient temperature was so high that he was sweating. This demonstrates the value of using a high temperature in order to exaggerate the measurements. The two graphs marked

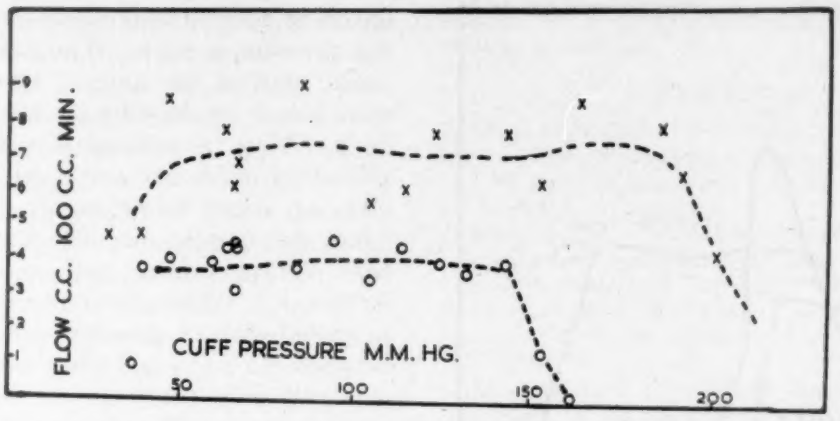

FIG. 7. Graphs of two experiments on a patient with hypertension, relating blood flow to cuff pressure. The upper curve was taken soon after admission when his sitting blood pressure was 220/160 mm. Hg, the lower after treatment, when the blood pressure was 170/130 mm. Hg.

8.0 and 4.5 were obtained on different occasions but under similar conditions. This shows the marked variability that may occur between different experiments, especially where the ambient temperature is that usually adopted for studies of blood flow.

One important factor that had to be taken into consideration in examining this phenomenon was to what extent are the results dependent upon high systolic and high pulse pressures. In Figure 7 are records from two experiments on a patient with hypertension. It will be observed that, although high flow values are recorded, there is a plateau and no significant increase in blood flow when cuff pressures rising from 50 to above 150 mm. Hg are applied. The lower record was obtained in the same patient following treatment.

THE CALCULATION OF AN INDEX

To express this qualitative observation with numerical values two methods of calculating an index are considered.

Index 1: As in normal subjects with the arm in the vertical position veno-occlusive pressures of 50 or 70 mm. Hg provide the same flow values, it is suggested that at 50 mm. Hg there has been a complete occlusion of the veins. It has been previously demonstrated that such pressures have no compressing effect upon normal arteries.[5] There is no reason to suggest that in cases of hypertension or aortic regurgitation occlusion of the veins is not also complete with cuff pressures of 50 mm. Hg. Therefore, the increase in blood flow that occurs with pressures higher than 50 mm. Hg is not likely to be due to any further increase in compression of the veins, and is probably due to an effect of the cuff pressing on the arteries. On the basis of this assumption, the alterations in flow that occur with pressures higher than 50 mm. Hg may be considered as due to an influence of the cuff pressure on the arteries.

Assuming that a pressure of 50 mm. Hg provides a blood flow approximating that of a "resting" limb, then, by comparing the maximum flow value obtained with higher cuff pressures, a ratio of the "maximum" over the "resting" value would give an indication of the proportionate increase in flow that occurs due to the valve-like action of the cuff and, conse-

TABLE I

Indices of Forward and Regurgitant Limb Flow in Patients with Aortic Incompetence, Compared with a Normal Patient and a Patient with Hypertension

Condition and Blood Pressure (mm. Hg)	Index 1: Maximum Flow/Flow at 50 mm. Hg	Index 2: Increase in Flow/100 mm. Hg. Increase in Cuff Pressure
Aortic incompetence		
145/20	2.58	13.0
220/25	2.90	6.7
180/30	2.25	12.5
160/60	1.10	1.6
140/35	2.03	8.5
120/30	2.88	7.0
180/45	1.50	4.4
Normal		
115/70	1.10	0.1
Hypertension		
200/120	1.10	0.5

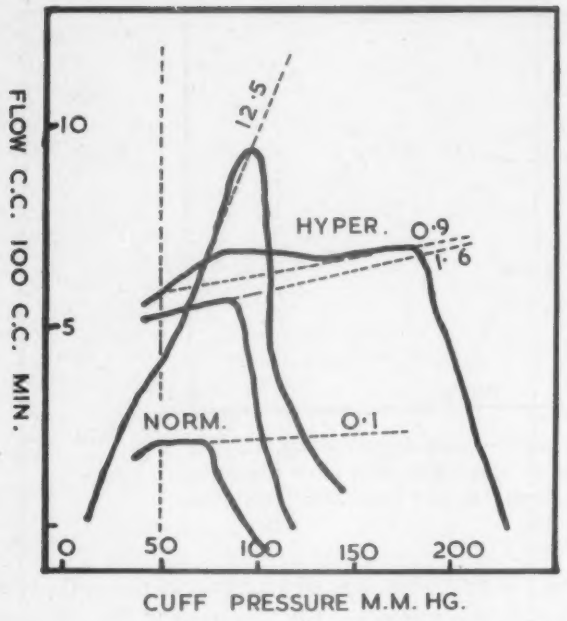

FIG. 8. The figures represent indices calculated as described in the text (see section on index 2). The curves with indices calculated as 12.5 and 1.6 were recorded in patients diagnosed clinically as having aortic incompetence. The curve marked "hyper," with an index of 0.9 is from a patient with hypertension. That marked "norm," with an index of 0.1, is from a normal subject.

quently, some indication of the degree of back flow. The first index was calculated on the basis of this assumption. In Table I the values in the second column (Index 1) were calculated by this method. The first figure of 2.58 suggests that, without the cuff acting like a valve, for every 2.58 cc. of forward flow there is a backward flow of 1.58 cc., leaving a net forward flow of 1 cc.

Index 2: The second index was calculated as follows: A line was drawn from the flow value recorded at 50 mm. Hg to the maximum value and the results were expressed as an increase in the blood flow rate per 100 mm. Hg cuff pressure (Table I, Index 2). The figures in Figure 8 are indices calculated in this manner for a series of conditions described in the legend.

Table I presents the indices from a series of patients with aortic regurgitation and, for comparison, a patient with hypertension and a normal subject. The first column is the blood pressure recorded by the auscultatory method on the arm of the subject when seated.

COMMENTS

It is clear that a pneumatic "valve" cannot act as well as a mechanical valve like that in the normal aorta. A considerable amount of work has to be done to force blood past the cuff when the pressure is high. This, of course, is not unlike that of the normal aortic valve where work has to be done by the heart before it will open. Thus, a pneumatic cuff acting like a valve may mimic the aortic valve in a condition such as aortic incompetence. On the other hand, the closure may be quite different and here the pneumatic cuff may be relatively inefficient. Whereas the aortic valve will tend to close when a pressure difference develops between the aorta and ventricle, the pneumatic cuff will only compress the artery when the arterial pressure has fallen below that in the cuff, by which time a significant amount of regurgitation may have occurred. It is interesting to note the large increase in flow that can be obtained on occasion by using an inefficient valve such as a pneumatic cuff.

To estimate the clinical value of this technic a group of patients with rheumatic aortic valve lesions were examined in Philadelphia. There was, in these patients, both stenosis and regurgitation. The results did not demonstrate the marked regurgitation observed in patients from Jamaica with syphilis where stenosis was not an obvious feature. It may be that one pattern of pulse pressure may produce results different from that of another pattern. It has been shown[6] that a broad and rounded pulse will have considerably more energy available at its peak to penetrate a compressed segment of an artery than the narrow, spiked, classic Corrigan's pulse.

It cannot be claimed that the method, as at present designed, has proved itself to be of much value clinically. For this reason, a pulsating cuff is being developed which will instantaneously release and apply pressure at any point in the pulse cycle and thus obstruct regurgitation more efficiently. Possibly this will provide a safe and more efficient method of measuring aortic regurgitation.

SUMMARY

It has been noted that under certain conditions a standard sphygmomanometer cuff may act as a valve on the peripheral blood vessels. A pneumatic cuff was employed as a valve on the brachial artery in aortic incompetence, and by obstructing the regurgitant blood a means for measuring its volume was devised. The principle on which this method is based is that of using a special type of sphygmomanometer cuff which at certain pressures exerts a valve-like action on the brachial artery.

In aortic incompetence the cuff prevents some of the backward flow, thus increasing the forward flow. This increase in forward flow, measured plethysmographically, is used as a basis for calculating indices of regurgitation. The essential feature of the technic is the measurement of forearm-hand blood flows by venous occlusion plethysmography with the limb in the upward and vertical position, and at high ambient temperatures of 30 to 32°C. A high degree of regurgitation may be indicated by this technic.

Acknowledgment

Acknowledgment is gratefully made to the staff of the University College Hospital and the Kingston Public Hospital, who allowed me to use their subjects, to Professor J. Scott and Drs. C. Bailey and H. Goldberg of the Hahnemann Medical College, Philadelphia, Pennsylvania, who placed facilities and clinical material at my disposal, and to the Medical Research Council of Great Britain for assistance.

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Factors Affecting the Pulmonary "Capillary" Pressure*

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THE determination of "pulmonary capillary" or, more correctly "pulmonary wedge" pressure, as obtained by a cardiac catheter wedged in a branch of a pulmonary artery, has been of great value in the study of cardiopulmonary hemodynamics, particularly in the assessment of mitral valvular and left ventricular disease.[1–5] Recent studies have demonstrated the similarity between such pressures and those obtained by direct left atrial puncture.[6,7] These pressures are elevated in the presence of mitral valvular disease or left ventricular failure. Pulmonary wedge pressures in patients with primary pulmonary disease, including pulmonary emphysema and cor pulmonale, have been reported to be normal[8] despite the presence of pulmonary artery hypertension and hence an elevation of calculated pulmonary arteriolar resistance. It is believed that the factors influencing the pressures obtained via cardiac catheter wedged in the pulmonary vascular bed have not been well defined.[7] It is the purpose of the communication to present further data on pulmonary capillary pressure-flow relationships obtained utilizing the method of temporary unilateral pulmonary artery occlusion. The general results of such studies in a group of control subjects[9] and in patients with chronic pulmonary disease[10,11,17] have been previously reported. The effect of exercise will also be considered.

METHODS

The studies being reported were carried out on twenty-seven patients, two control, four with primary myocardial or endocardial disease, thirteen with diffuse bilateral pulmonary disease, three with localized pulmonary disease and five with both pulmonary and cardiac disease. In Table I these patients are grouped according to clinical diagnosis.

Cardiac catheterization was carried out in the usual manner in a resting postabsorptive state. Light sedation (usually secobarbital 0.1 gm.) was used. A triple lumen cardiac catheter with an inflatable cuff on the middle lumen was introduced into the median basilic vein and advanced under fluoroscopic control into either right or left pulmonary artery into a wedged position. After measurement of wedge and pulmonary artery pressures, the catheter was withdrawn into the main pulmonary artery subdivision and the cuff inflated with dye, again under fluoroscopic control. Main pulmonary artery and distal pressures and blood samples were obtained. Pressures in the pulmonary artery were recorded using a Sanborn electromanometer and direct writing Sanborn polyviso recorder. Peripheral arterial pressures were recorded by Statham strain gauge manometers. Blood samples were analyzed by the spectrophotometric method of Hickam and Fraser[12] or manometric technic of Van Slyke[13] for oxygen content to verify the position, fully oxygenated blood being obtained in both wedge and distal locations. In four patients with clinical diagnosis of emphysema, pressures were measured during exercise with either a wedged catheter or beyond an inflated balloon, together with the pulmonary artery pressure.

Pressures in the pulmonary artery are given as systolic and diastolic in mm. Hg. The distal and wedge pressures are recorded as the highest level during expiration and the lowest during inspiration. The curves recorded showed damping in many cases making it difficult to identify A, C and V waves. Exercise consisted of straight leg-raising at a constant rate for four to six minutes. Pressures were recorded during the last minute of exercise.

RESULTS

Pressures: The data presented in Table II show good agreement between pressures obtained by a wedged catheter and distal to an

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TABLE I
Pulmonary Capillary and Artery Pressures

Patient	Age (yr.)	Sex	Pulmonary Capillary				Pulmonary Artery		Pulmonary Artery Occluded		Clinical Diagnosis
			Wedge		Distal						
			Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration	
Control Subjects											
1. D. S.	43	M	5	9	3	9	18/5	22/9(11)	26/8	30/13(18)	Normal
2. E. S.	20	M	0	8	1	6	24/8	27/10(15)	34/14	36/17(22)	Normal
Patients with Pulmonary Disease, Diffuse											
3. J. M.	52	M	0	8	5	10	20/8	28/14(14)	32/8	42/16(23)	Tuberculosis, bilateral
4. E. D.	56	M	3	7	−2	10	30/12	40/20(22)	39/15	50/25(30)	Silicosis, carcinoma of right lung
5. T. M.	37	M	4	12	0	8	18/6	24/14(14)	26/8	35/15(22)	Bullous emphysema
6. W. P.	23	F	7	11	6	12	14/5	16/7(10)	28/10	31/12(19)	Sarcoidosis
7. M. H.	45	M	5	25	10	30	45/18	65/32(36)	55/18	70/34(38)	Bronchiectasis
8. W. T.	54	M	5	15	2	12	25/16	35/22(22)	50/19	58/26(36)	Silicosis
9. W. D.	35	M	−5	9	−3	13	18/3	30/18(18)	39/20	60/28(34)	Bullous emphysema
			8	18	8	17	22/11	38/26(23)	32/10	56/28(30)	
10. E. S.	39	M	1	10(8)	3	12	26/14	32/19(22)	41/16	50/24(34)	Emphysema
11. L. G.	70	M	−6	3	−3	10	34/14	46/19(25)	52/17	68/24(36)	Bronchiectasis
12. L. D.	49	M									
12/2/54			6	18	−4	10	38/18	44/24(30)	62/25	70/35(47)	Bullous emphysema
11/20/53					7	21	28/26	46/29	30/17	50/32(36)	
13. R. H.	41		8	20	−6	12	30/20	55/30(37)	54/28	68/40(45)	Cystic lung disease, cor pulmonale
14. M. W.	43	F	−3	7	−3	7	14/6	24/16(14)	20/12	30/21(18)	Emphysema, cor pulmonale
15. M. H.	55	F	8	20	6	20	72/28	82/33(40)	81/30	92/32(46)	Emphysema, cor pulmonale
Patients with Pulmonary Disease, Localized											
16. E. H.	52	F	12	16	5	12	28/14	33/19(22)	36/16	42/20(26)	Tuberculosis, upper lobe of right lung
17. C. K.	36	M	−5	8	−2	17	22/6	32/14(19)	26/8	34/20(22)	Tuberculosis, left lung
18. J. B.	26	M	0	9	0	10	22/7	26/12(16)	42/16	47/22(30)	Tuberculosis, left lung
Patients with Cardiac Disease											
19. E. M.	55	F	22	30	24	35	54/25	58/30(38)	84/32	90/36(55)	Mitral and aortic stenosis
20. A. P.	38	F	15	35	15	38	80/38	98/42(56)	80/40	100/43(55)	Mitral insufficiency
21. J. R.	26	M	25	30	20	25	88/40	100/52(68)	102/50	110/62(80)	Mitral stenosis
22. R. H.	43	M	30	40	25	30	60/30	70/35(45)	62/35	70/45(50)	Mitral stenosis
Patients with Combined Cardiac and Pulmonary Disease											
23. E. O.	25	F	18	35	12	43(28)	47/30	50/34(42)	54/25	58/32(40)	Myocardial and pulmonary sarcoidosis
24. W. B.	47	M	15	38	12	30	60/30	78/35(50)	55/26	54/32(42)	Mitral stenosis, bronchiectasis
25. C. S.	55	M	10	30(21)	12	25	58/26	64/30(42)	56/28	62/32(42)	Mitral stenosis, emphysema
26. O. B.	66	F	12	28(18)	0	18	32/10	46/22(28)	50/18	65/28(38)	Aortic insufficiency, tuberculosis
27. F. E.	71	M	5	12	3	10	27/10	34/15(22)	32/18	40/23(27)	Aortic insufficiency, carcinoma of lung

NOTE: Figures in parentheses represent the mean.

occluding balloon in a major subdivision of the pulmonary artery. These technics are, in fact, quite similar since, in either case, the blood flow has been interrupted in that segment of lung either by the catheter itself or by the special cuff. Pressures thus obtained are undoubtedly lower than actual unoccluded pulmonary capillary pressure.[4] Figure 1 demonstrates the similarity between the wedge, distal and left atrial pressures in Case 9.

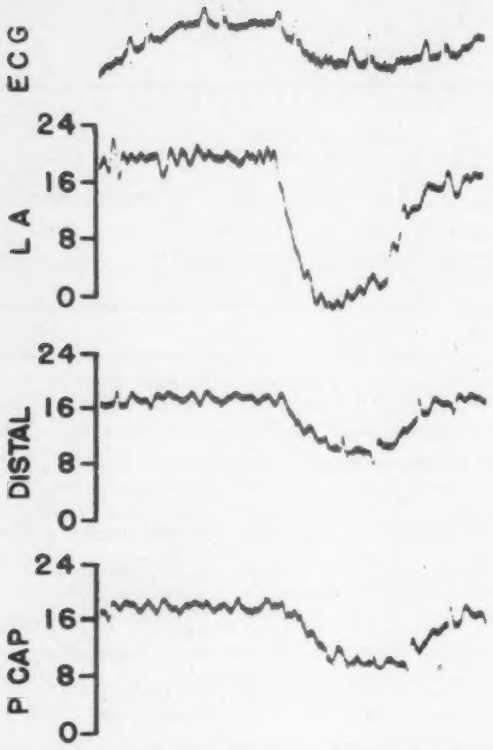

FIG. 1. From above down are shown simultaneous electrocardiogram, left atrial pressure, pressure distal to an occluding balloon in a main branch of the pulmonary artery and a wedge pressure. Note similarity in contour and respiratory variation. *Left*, expiration. *Right*, inspiration.

Pressures were normal in the control group and elevated in those with cardiac disease whether isolated or associated with pulmonary disease. The wedge pressure was also normal in isolated pulmonary lesions. The most interesting results were obtained in those with diffuse pulmonary disease (Table I). The pressures recorded show the expected respiratory variation; however, the vascular pressures during expiration frequently reached abnormally high values. Since the expiratory phase is most pronounced and prolonged in such patients, the mean wedge or distal pressure was elevated. This finding was in contrast to expected normal pressures in emphysematous states.

Many investigators have observed difficulty in obtaining wedge pressures in patients with pulmonary hypertension, particularly when secondary to mitral stenosis. This occurred in several of our patients as well; however the pressure beyond the inflated balloon appeared to be commensurate with the degree of heart failure due to mitral valvular disease. Thus, this technic can be used to estimate capillary pressure when ordinary wedge pressures are unobtainable. In several instances, a true wedge pressure was obtained when the catheter balloon was partially inflated, the catheter then carried distally by a "sail-in-the-wind" effect, and the cuff then deflated.

An interesting observation during the course of these studies was the difficulty in aspirating wedged blood samples. This problem was encountered rarely in normal patients or in those with elevated left atrial pressure but was quite common in those with emphysema, particularly if resting pulmonary artery hypertension was present.

In several patients with pulmonary disease, exercise was also carried out. The results are shown in Table II. It can be seen that there may be a considerable rise in measured pressure with exercise (Table II and Fig. 2). Pulmonary artery pressure rises as well in such cases as shown by others.[14–16] Since blood flow has been interrupted in the region of the obstructing catheter, it is obvious that factors other than the cardiac output and arteriolar resistance are responsible for the apparent increase in pressure. In the cases presented, the apparent rise in pulmonary artery pressure can be explained, at least in part, by an increase in measured wedge or distal pressure.

TABLE II
Effect of Exercise in Four Cases of Pulmonary Disease

Patient	Control		Exercise	
	Distal or Pulmonary Capillary or Wedge	Pulmonary Artery	Distal or Pulmonary Capillary or Wedge	Pulmonary Artery
T. B.	9/0	38/11 (22)	23/7	70/25 (42)
C. E.	16/0	40/15 (28)	28/5	60/25 (38)
H. M.	10/0	34/10 (21)	32/15	52/24 (38)
E. H. Occluded	12/5	35/18 (27)	20/10	45/22 (33)
Unoccluded	16/12	30/15 (23)	30/20	40/20 (30)

NOTE: Figures in parentheses represent the mean.

COMMENTS

It is apparent from the data presented that temporary unilateral pulmonary artery occlusion may produce distal to an occluding balloon

the same conditions that are obtained by wedging a cardiac catheter into the pulmonary artery. Under these circumstances, flow through the local region or entire lung is arrested and the recorded pressures beyond the occlusion reflect left atrial pressure. Extravascular or intrapulmonic pressure changes may cause marked respiratory variations. The latter are small in normal subjects and in patients with mitral valve disease or left ventricular failure with high left atrial and pulmonary venous pressure. The same is true for isolated pulmonary lesions. In emphysema, however, intrapleural and intraalveolar pressures may reach considerably elevated expiratory levels, due to the existing airway obstruction.[18,19] Under these circumstances, the intrapulmonic pressure may greatly influence the recorded intravascular pressures causing marked respiratory variation and an increase in mean pressures. If exercise is superimposed, greater intrapleural pressures are generated in the emphysematous patient causing an apparent further increase in pulmonary vascular pressure. It is our belief that this factor is most significant in causing the rise in pulmonary artery pressures observed in patients with emphysema rather than inferring involvement of the pulmonary vasculature. Studies in patients having emphysema with pulmonary hypertension have shown that an increase in pressure with increased flow is not always obtained.[10,11] Exercise may well cause further increase.[14,20] In view of these findings, it would seem inadvisable to calculate changes in pulmonary resistance using an assumed or static capillary pressure since an apparently increased gradient PA/PC may not be an actual or effective one.

In further support of this contention was the repeated difficulty in aspirating blood samples from a wedged catheter or distal to an occluding balloon. It is suggested that with cessation of flow in the obstructed segment, the intravascular pressure is lowered beyond the critical point[21,22] and the increased extravascular pressures collapse the small pulmonary arterioles and capillaries creating a "retrograde block."

In patients with mitral stenosis, the pulmonary hypertension may vary from slight to marked. This disparity between left atrial pressure and pulmonary artery pressure has been puzzling and is usually ascribed to pathologic changes in the pulmonary arterioles.[23,24] In several of our cases, however, marked respiratory variations in pulmonary capillary or

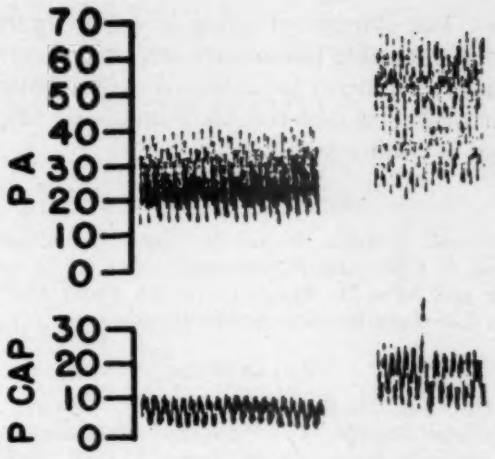

FIG. 2. Pulmonary artery pressures are shown above and wedge pressures below, before (*left*) and after (*right*) exercise. Slow paper speed.

distal pressures were noted of the type seen in pulmonary emphysema suggesting that an increased intrapleural pressure was present because of airway obstruction. This obstructive phenomenon is most obviously seen in patients with cardiac asthma. Increase in bronchomotor tone[19] may well be a protective mechanism under these circumstances by increasing intra-alveolar pressure and thus increasing the extravascular resistance to pulmonary blood flow.

SUMMARY

1. Pressure in a major branch of a pulmonary artery beyond an occluding balloon invariably fell to pulmonary capillary levels and resembled the latter closely.

2. Distal pressures correlated well with pulmonary capillary pressures and were normal in control patients and elevated in those with left ventricular failure and/or mitral disease.

3. In pulmonary emphysema, the distal and pulmonary capillary pressures varied greatly with respiration and occasionally reached considerably elevated levels during expiration. Exercise in such patients caused a significant apparent rise in wedge pressure.

4. The role of bronchomotor tone and intra-alveolar and intrapleural pressures are discussed with regard to their possible role in regulating pulmonary artery pressure.

5. The method has been of value in obtaining pulmonary capillary or distal pressures in those individuals, particularly with pulmonary artery hypertension, in whom such pressures were otherwise unobtainable.

6. The danger of using a static figure or zero in obtaining pulmonary arterial-pulmonary capillary gradients for calculation of pulmonary resistances, particularly in pulmonary emphysema, is emphasized.

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The "Straight Back" Syndrome

A New Cause of Pseudoheart Disease*

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THE purpose of this paper is to present a heretofore unrecognized deformity of the chest causing pseudoheart disease. I prefer to call this the "straight back" syndrome. It is a condition that seems to represent a congenital loss of the normal, gentle kyphotic curve of the upper dorsal spine so that the flattened palm of the examiner's hand may be superimposed upon the area without deviation of the fingers. The condition would seem to be the opposite of "funnel chest." Instead of deformity affecting the sternum, there is an incomplete inward displacement or flattening of the upper dorsal spine.

The syndrome, which seems congenital in origin, may produce pseudoheart disease in one of two ways. First, as in funnelling of the sternum, there is a decrease in the anteroposterior diameter of the chest, noticeably in the region of the upper dorsal spine. This causes false enlargement of the heart in the frontal view, particularly in the great vessel area and waist of the heart, since there is compression of these structures between the sternum anteriorly and the straightened, somewhat inwardly displaced dorsal spine posteriorly (example, Fig. 7). The second means of producing pseudoheart disease seems to be by compressing or kinking the great vessels. This distortion appears to produce mechanical murmurs in systole located near the base of the heart or over the precordium. Both types of pseudoheart disease appear to be completely benign in nature. Rarely is the defect found without either false enlargement of the heart or mechanical murmurs.

OTHER CAUSES OF PSEUDOHEART DISEASE

The straight back syndrome is only one of several forms of pseudoheart disease. For some time it has been recognized that false variations in heart size on x-ray examination are induced by physical phenomena. These include variations in depth of respiration, type of body build, the phase of cardiac systole at the time of the roentgenogram, changes in the position of the body, presence or absence of abdominal masses (pregnancy), and many others.[1,2] In obese or mesomorphic subjects the heart is usually transverse and may at times appear enlarged. It may actually measure "enlarged" by transverse diameter measurement in some cases. On the other hand, the vertical heart may be subnormal in size, and sometimes microcardia may be seen in thin, asthenic subjects.

Less commonly remembered is the effect of respiration. During inspiration, the heart normally moves anteriorly toward the midline, decreasing the retrosternal space (Fig. 1). During expiration the heart elevates and moves posteriorly and to the left and appears larger. If the film is not taken during adequate inspiration, the heart tends to appear "squat-shaped," with enlarged measurements. Such an expiratory film should be easily recognized by the closeness of the interspaces, raised diaphragms and increased bronchovascular markings (Fig. 1). Confusion with true enlargement of the heart can also be avoided by counting the number of anterior ribs that appear above the diaphragmatic level. Usually six should be seen.

Other situations affecting heart size on x-ray examination may involve technical errors. If the patient is allowed to hold his breath excessively long before the picture is snapped, an unconscious performance of a Valsalva maneuver may occur. As the breath is held, venous inflow into the heart is reduced by the increased intrathoracic pressure. The heart meanwhile continues to pump, pumping out the blood it contains and becoming progressively smaller

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FIG. 1. Mechanical factors causing variations in cardiac size in the same patient.

with each beat. In this way, a truly enlarged heart may appear normal or actually small in size if the breath is held for a longer period than usual during routine x-ray examination of the chest (Fig. 1).

Changes in position also affect the heart. In fact, the mediastinum is ordinarily quite mobile.[3] Routine chest films are therefore always taken with the patient erect. In recumbent posture the heart decreases in length, increases in width and the vascular shadows at the base of the heart widen. In pregnancy, of course, the elevated diaphragm and increased blood volume cause the heart to appear considerably widened.

Perhaps the most frequent source of error in heart mensuration is the pericardial fat pad. Located as a triangular shadow at the apex of the heart, the fat pad is of no clinical importance. The pad should be excluded from transverse diameter measurements. However, it cannot always be identified on routine chest films and is best seen fluoroscopically when it is present.

Some other causes of pseudoheart disease include the various heart displacements created by congenital deformities of the chest or by acquired diseases of the lungs. Deformities of the chest may not only displace, but also distort both the heart and the great vessels. For instance, in scoliosis of the dorsal spine the spine usually deviates to the right, causing displacement of the heart to the left. Funnel chest, on the other hand, decreases the anteroposterior thoracic diameter, squeezing the heart between the sternum and the spine, displacing it somewhat to the left and pancaking its frontal view into wide measurements.[1,4] Conversely, the presence of emphysema may obscure enlargement of the heart due to the forced vertical position and elongation of this structure. Oppositely, anything causing elevation of the diaphragm, such as gas, herniation or paresis, may cause a horizontal position of the heart and apparent enlargement of the heart.

Therefore, determination of heart size and its relationships within the chest is an essential part of every physical examination. Ascertaining heart size, however, is not always possible on routine examination. There may not be a distinct point of maximal intensity of the apical beat. On the other hand, inaccuracies of outlining the heart by percussion are well known. Confusion may also occur during the examination if the heart is actually displaced rather than enlarged. At this point, a routine chest film is usually obtained. In fact, when the heart or great vessels are under particular scrutiny, fluoroscopy should be considered an important part of the patient's survey.[5,6] All views of the heart are then possible, and dynamics are observable. The routine x-ray film of the chest, however, is not an infallible means for determining heart size. The transverse diameter, being the more common measurement employed in the United States, actually involves three heart chambers, and is noticeably inaccurate in borderline cases. Enlargement in this transverse diameter is frequently a late occurrence. Anterior or posterior enlargement usually occurs well before transverse widening becomes evident. Lateral views may show this. Conversely, causes of false enlargement of the heart in the frontal view are usually overlooked entirely unless lateral films are taken in these cases.

Clinical Examples of Straight Back Syndrome

In the short period of three years in a moderate size city, we have gathered nine cases of straight back syndrome which had been masquerading as heart disease. The true incidence in the general population has yet to be determined.

The degree of deformity varied from mild cases with torsion murmur and no enlargement to severe cases with actual widening of the heart shadow. The milder cases (Figs. 2 and 3) were more frequent and usually presented slightly

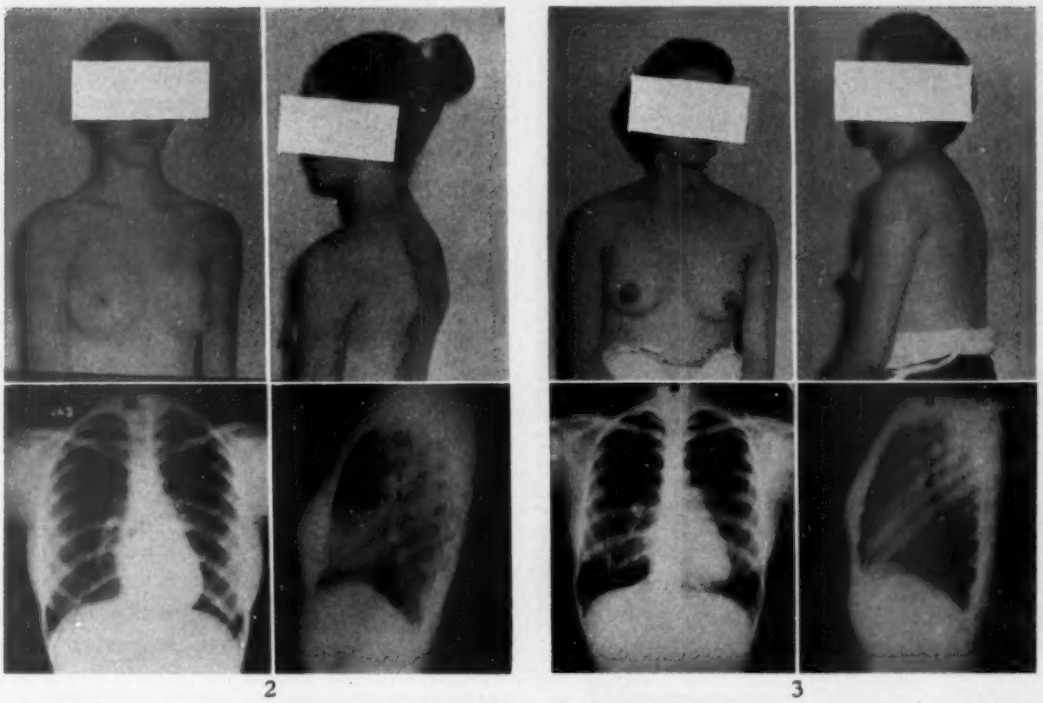

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FIG. 2. Basal systolic murmurs were apparently induced by the decreased sternovertebral depth and narrowed retrosternal space. Some respiratory aggravation of the murmur was also demonstrable.

FIG. 3. Straight back deformity with associated flaring of the ribs and filling of the waist of the heart. Mitral stenosis was suspected from the heart sounds before the lateral chest film was obtained. The deformity in this case was insufficient to produce cardiac compression.

harsh, late systolic murmurs over the base of the heart accompanied by increased pulmonic closure sounds by auscultation, and "filling" of the heart waist on x-ray examination. Fluoroscopically, this filling represented rotation and impingement of the pulmonary conus against the retrosternum in the area of the murmurs. The straightened dorsal spine seemed to be a constant clinical finding in these cases. Actual physical grooving or funnelling of the spine rarely occurred (Fig. 4).

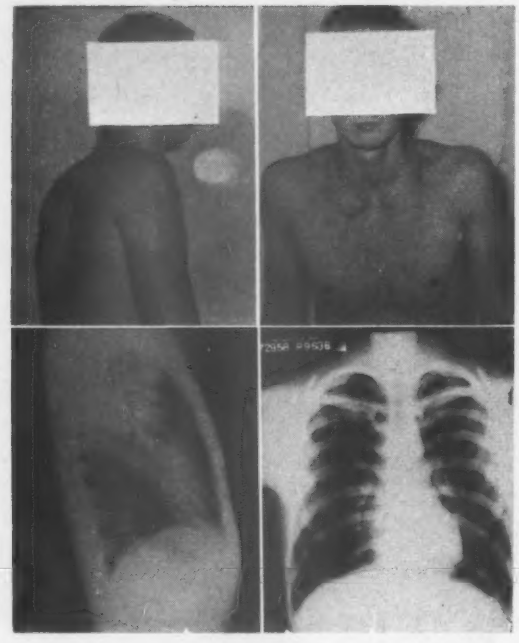
One of the patients (Fig. 5) had been refused life insurance because of a persistent harsh systolic murmur at the base of the heart. Rheumatic fever had first been suspected and as a result she spent six weeks at bedrest. The mechanical defect of straight back syndrome was present, and the usual pathological causes for this murmur were excluded by catheterization and other appropriate tests. A diagnosis of benign murmur of no consequence was made. As a result, the insurance company awarded the policy free of riders and restrictions.

Another patient (Fig. 6), in whom a diagnosis of an interventricular septal defect had been made previously, had been living with the delusion of serious heart disease all of her adult life. She had purposely avoided pregnancy, had limited her recreational activities and was leading a rather secluded life. Clinical studies and cardiac catheterization showed no abnormalities.

One patient (Fig. 7) had been refused employment at one of our larger manufacturing plants because of an enlargement of the heart. A lateral x-ray film of the chest was taken when a straightened dorsal spine was noticed on routine cardiovascular examination. Heart compression was definite. The apparent enlargement was shown to be false and the patient was accepted for employment.

COMMENTS

Perhaps the best way of confirming false enlargement of the heart on routine x-ray films of the chest is the demonstration by lateral view of a narrowed chest depth with resulting heart compression or "pancaking."[1] Normally, the degree with which the heart impinges on the retrosternal space in the lateral view depends upon the shape of the thorax, the degree of inspiration (at which time it is closer to the sternum) and the amount of pericardial fat (obesity). Now in-



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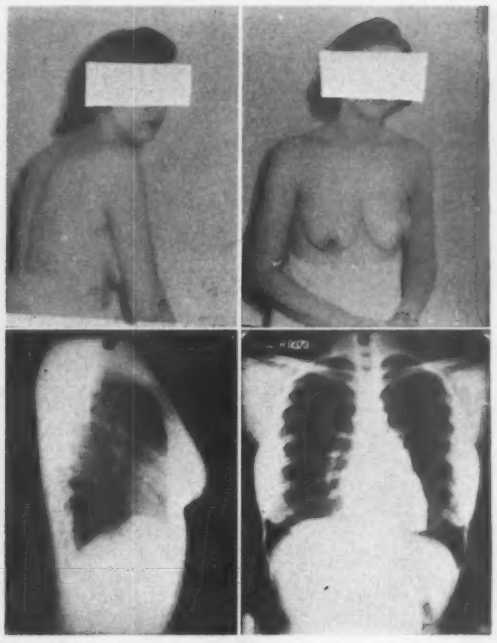

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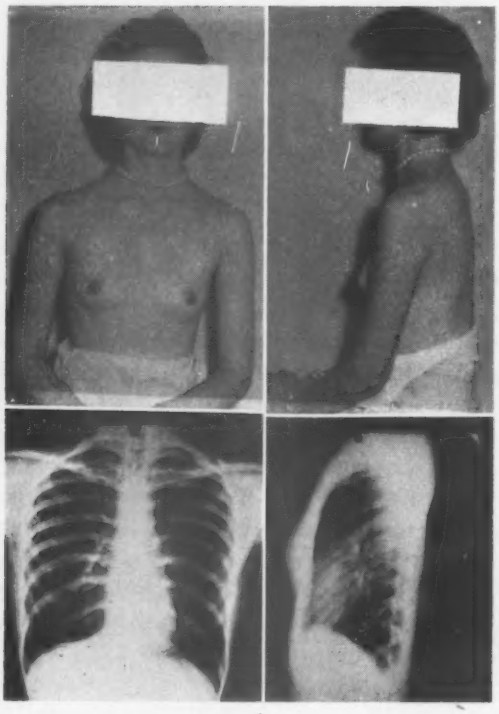

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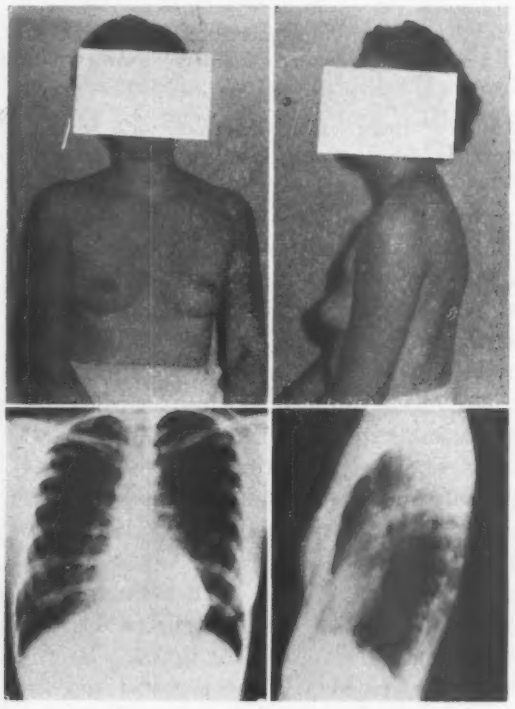

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FIG. 4. Unusual case with associated funnelling of the spine and mild pigeon breast. The latter apparently acted as a compensatory mechanism and no compression phenomena could be demonstrated.

FIG. 5. Moderate mediastinal compression caused both slight cardiac enlargement and an alarming murmur. The murmur resembled aortic stenosis.

FIG. 6. Associated murmur resembled an interventricular septal defect. The degree of straightening was not sufficient for the production of pseudocardiomegaly.

FIG. 7. Straight back syndrome with associated marked mediastinal compression and pseudocardiomegaly.

cluded in this list is the straight back syndrome in which the retrosternal space is obliterated.

Frequently, the degree of straight back deformity is insufficient to widen the heart shadow, but is sufficient to compress the aortic arch or to impinge upon the main pulmonary trunk, creating mechanical murmurs. As already mentioned, the pulmonary conus lies against the inner surface of the sternum, which may then act as a "sounding board" in some cases. The aorta, anchored at the root of the heart and at the diaphragm, is subject to torsions at the level of its arch and could conceivably create murmurs.[2,7] Furthermore, in the straight back syndrome, the aorta tends to descend completely anterior to the spine and would appear to be a more mid-line structure than normal (Fig. 8). However, the exact etiological mechanism of the murmur found in this syndrome is not clear.

Many of these spinal defects might begin in the eighth week of fetal life before ossification occurs in the bodies of the vertebrae. It seems conceivable that failure in development of the normal kyphotic curve of the upper dorsal spine could be a common occurrence when compared to multiplicity of the many other spinal defects that frequently appear.[8] Perhaps the completely straightened spine that characterizes the normal infant fails to develop the expected postural curves of adulthood for other reasons. Perhaps, also, the degree of deformity is limited by the thoracic cage itself because of the splinting effect of the ribs upon movements in the dorsal spine.

Several other factors could also have a bearing upon the resulting enlargement of the heart. Perhaps there could be an associated persistence of the globular infantile heart in the adult silhouette. Also, the depth of the chest may fail to increase as the body in general continues to grow. Furthermore, the cardiac silhouette found during recumbency often resembles that found in the straight back syndrome. The cardiac silhouette widens considerably in many patients when the gravitational effects of recumbency cause the heart and great vessels to rest toward the dorsal spine posteriorly.[9] Functional vascular murmurs might conceivably increase during recumbency for similar reasons. The straight back syndrome could present a similar situation, due to the anterior displacement of the dorsal spine.

Although it is known that various deformities of the chest may result in cardiorespiratory failure from distortion of the heart or kinking of the great vessels, we have not observed any tendency to decompensation with this new syndrome. Perhaps this can be likened to the frequency of heart failure in kyphoscoliosis[10] compared to its rarity in pectus excavatum.[11]

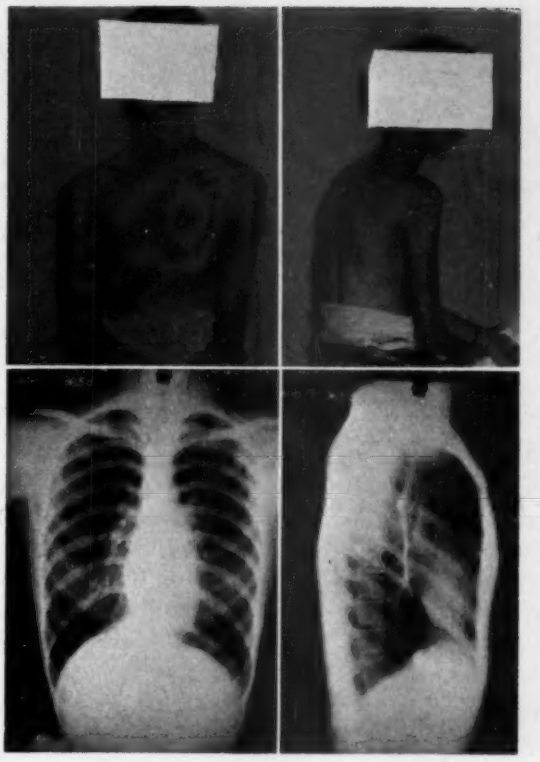

FIG. 8. The aorta often descends anteriorly to the spine, apparently as a mid-line structure.

SUMMARY

We have presented a new syndrome of heart disease that has not been found recorded in the literature heretofore. We prefer to call this the "straight back" syndrome. It consists of a congenital straightening of the upper dorsal spine which decreases the anteroposterior diameter of the chest at this level. Compression phenomena result which may either cause pseudocardiomegaly or cause mechanical murmurs. These murmurs are systolic in timing and would seem secondary to impingement or distortion of the great vessels. The condition is easily recognized by simple physical examination and usually confirmed when lateral x-ray views are taken. These defects are simple and may not be uncommon. Recognition of this condition may prevent a common form of iatrogenic heart disease.

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The Electrocardiographic Findings in Pulmonary Emphysema*

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ELECTROCARDIOGRAMS derived from the surface of the body are commonly considered to have originated from that aspect of the heart nearest to or underlying the electrodes.[1] Despite the fact that the body is not an especially uniform or homogeneous conductor, in most instances there is excellent correlation between the forms anticipated on theoretical grounds and the patterns actually obtained. This is so often true in normal subjects that observed deviations are explained in part or in whole on physical rotation of the heart around its various axes.[2] In some normal subjects, however, and in many patients with heart disease, movement of the heart sufficient in degree to explain observed patterns is anatomically impossible. It would seem that electrocardiographic position must, in some instances, be distinct from anatomic position. This is particularly true in patients with emphysema of the lungs who sometimes exhibit extraordinary electrocardiographic findings.

The material which forms the basis for this report was obtained in a Veterans Administration Hospital during a twelve-year period. The population of this hospital is almost wholly male with an incidence of chronic pulmonary disease greater than that encountered in most general civilian hospitals. Similar findings, however, have been encountered elsewhere, and there is no reason to believe that they are in any way unique or limited to men. The electrocardiographic patterns about to be described do not occur in all persons with emphysema and, although they are commonly seen without clinical cor pulmonale, this too is not invariable.

ELECTROCARDIOGRAPHIC FINDINGS IN EMPHYSEMA

The electrocardiogram of slight or early pulmonary emphysema is a normal record with an electrical axis approximating +90 degrees. It is quite like that seen in normal young or asthenic persons. The P waves, however, tend to be prominent and exhibit an axis close to +90 degrees. As emphysema progresses, the standard and commonly most of the precordial leads acquire S waves while the P waves become still larger. Later all standard and unipolar limb leads become equiphasic so that the mean axis of the QRS complexes becomes indeterminate and assumes a position at right angles to the frontal plane of the body. At the same time, the precordial leads through V_5, sometimes V_6, become negative so that the mean spatial vector, already perpendicular to the frontal plane, appears to be directed backwards. By this time, the P waves have commonly acquired the peaked P pulmonale configuration with an electrical axis which remains at +90 degrees. In our experience the pattern just described has been seen only in emphysema and is not, apparently, encountered in other conditions.

Having attained a position perpendicular to the frontal plane of the body the mean electrical axis of the QRS is capable of further rotation. When the positive terminus of the vector emerges above the electrical horizon, the mean axis can appear in a position of −60 to −90 degrees or more. A −90 degrees axis is considered to have been at +90 degrees in the past. This change, which probably requires a long time for its completion, has been observed to develop acutely without any apparent difference in cardiac position and generally occurs with pulmonary infections and probable consequent increase in emphysema.

Other electrocardiographic manifestations of emphysema include T wave abnormalities

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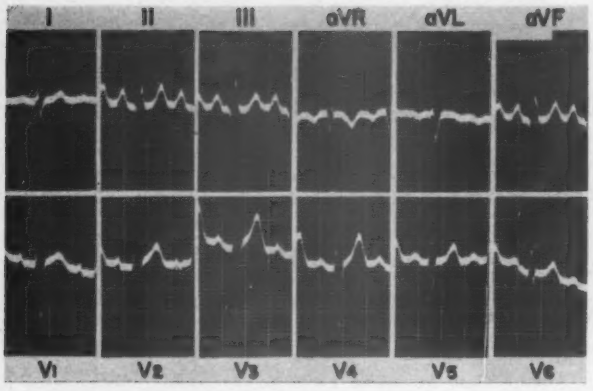


FIG. 1. Case 1. Electrocardiogram showing prominent P waves in emphysema.

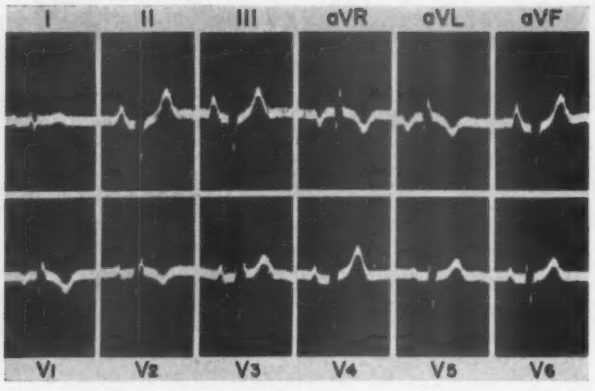


FIG. 3. Case 3. Electrocardiogram showing classic pattern of emphysema. Note similarity of leads aVR, aVL and V_1.

of right ventricular strain and the more classic but less common findings of right ventricular hypertrophy and right bundle branch block. Another unusual and baffling abnormality may mimic the pattern of myocardial infarction.

The examples which follow illustrate some of the characteristic findings in pulmonary emphysema. Several cases are briefly noted and one is described in more detail.

CASE REPORTS

CASE 1. A fifty-four year old railway expressman entered the hospital with a history of asthma and dyspnea for twenty years. The physical examination revealed a moderate deformity of the chest, low diaphragms and pulmonary emphysema. The one-second vital capacity was 700 cc.

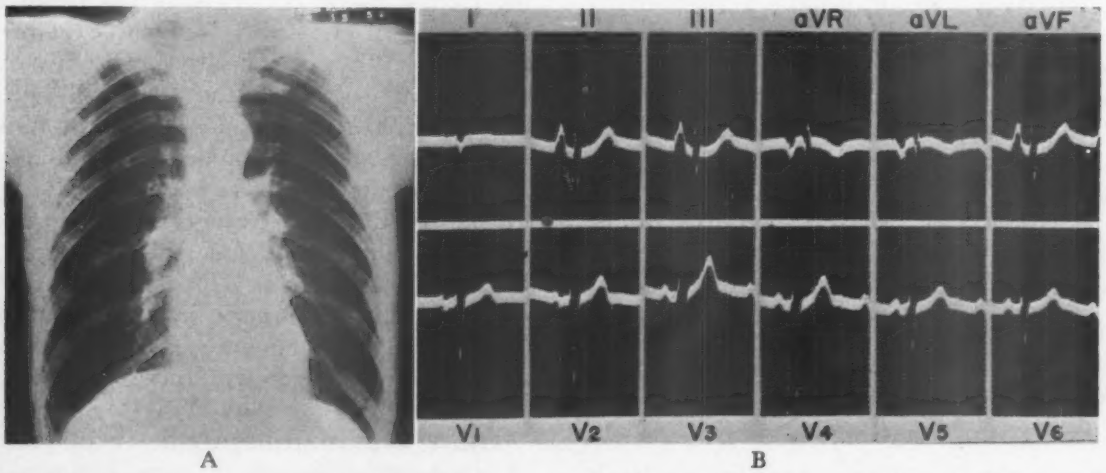
The electrocardiogram (Fig. 1) showed a QRS axis of +100 degrees and prominent P waves with an axis of +80 degrees. Were it not for the tall and peaked P waves this would be considered a normal record.

CASE 2. A fifty-eight year old man with chronic bronchitis had had frequent bouts of pneumonia and asthma since his early youth. There was extensive barrel deformity of the chest together with low but not flat diaphragms and a vertical heart of normal dimensions (Fig. 2). This man died six years later in congestive heart failure resulting from cor pulmonale.

The electrocardiogram (Fig. 2) exhibited the classic findings of emphysema. The QRS axis was perpendicular to the frontal plane and, judging from the negative complexes in all the precordial leads, directed backwards and rightwards. The P waves were abnormally tall in the limb leads and had an electrical axis of +90 degrees.

CASE 3. A fifty-seven year old man was admitted to the hospital with rheumatoid spondylitis, chronic bronchitis and emphysema. There was an extreme barrel deformity and almost complete fixation of the chest. There was no evidence of cor pulmonale. He died of bronchopneumonia not long after this record was obtained.

The electrocardiogram (Fig. 3) showed a QRS



A B

FIG. 2. Case 2. A, posteroanterior roentgenogram. B, electrocardiogram showing classic P and QRS patterns of emphysema.

axis which was at right angles to the frontal plane of the body and directed backwards. The P waves were abnormally tall in the limb leads and had an axis of +90 degrees. An interesting finding was the almost complete identity of appearance of leads aVR, aVL and V_1. This cannot be explained by unipolar methods.

CASE 4. A forty-seven year old man entered the hospital with chronic bronchitis, bronchial asthma and pulmonary emphysema. There was a characteristic deformity of the chest together with low, relatively fixed diaphragms.

The electrocardiogram (Fig. 4) showed a QRS axis of −60 degrees. The P waves were prominent and had an electrical axis of +80 degrees.

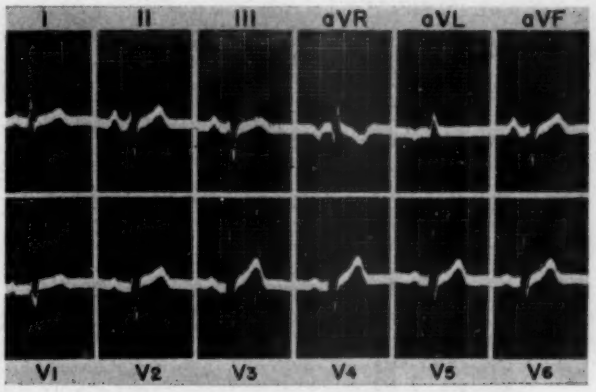


FIG. 4. Case 4. Electrocardiogram showing emphysema. Note QRS axis −60 degrees, prominent P waves.

CASE 5. A fifty-eight year old man was admitted to the hospital with chronic infectious bronchitis and emphysema (Fig. 5). There was no evidence of cor pulmonale when this examination was made. However, he died of this disease two years later.

The electrocardiogram (Fig. 5) demonstrated the classic changes of emphysema with the QRS axis perpendicular to the frontal plane and with predominantly but not wholly negative complexes in the chest leads. The P waves were not abnormally large but had an axis of +90 degrees.

CASE 6. A sixty-six year old former mechanic was incapacitated by the symptoms of a peptic ulcer, chronic cough, wheezing and shortness of breath. He was an emaciated man exhibiting a classic barrel chest deformity. His heart was of normal size (Fig. 6A).

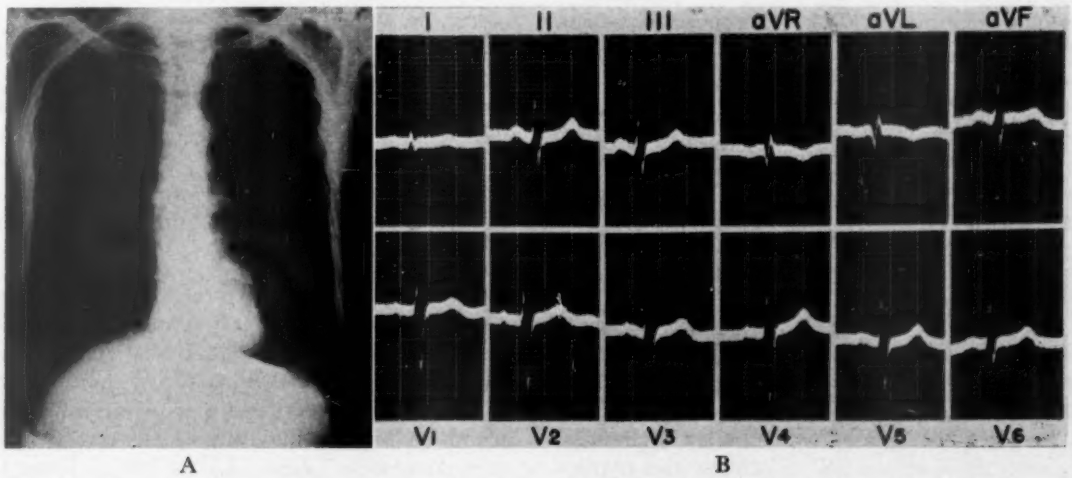
The electrocardiogram (Fig. 6B) showed a QRS axis which was largely perpendicular to the frontal plane but verging on −90 degrees. The prominent P waves had an axis of +70 degrees.

CASE 7. A sixty-two year old man had a history of pulmonary tuberculosis, chronic cough and asthma for many years. There were no symptoms of cardiac disease and the heart was not enlarged on examination. However, the cardiac silhouette appeared full on the roentgenogram and the right ventricular outflow tract was considered to be especially prominent (Fig. 7).

The QRS axis (Fig. 7) was at −90 degrees and, judging from the equiphasic precordial complexes, appeared to lie at right angles to the horizontal plane of the chest. The enlarged P waves, however, had an axis of +90 degrees.

An electrocardiogram was obtained on the patient following an interval of five years (Fig. 7C). The QRS and P axes were essentially unchanged but T wave inversions had occurred in leads V_1 through V_3, suggesting right ventricular strain. The P waves had also become larger. The almost completely negative QRS complex in aVF resembled the findings in an inferior myocardial infarction. When this record was made the patient was having symptoms of cor pulmonale.

CASE 8. A sixty-three year old man entered the hospital with a thirty year history of chronic bron-



A B

FIG. 5. Case 5. A, posteroanterior roentgenogram. B, electrocardiogram showing classic emphysema changes. Note identity of aVR and aVL.

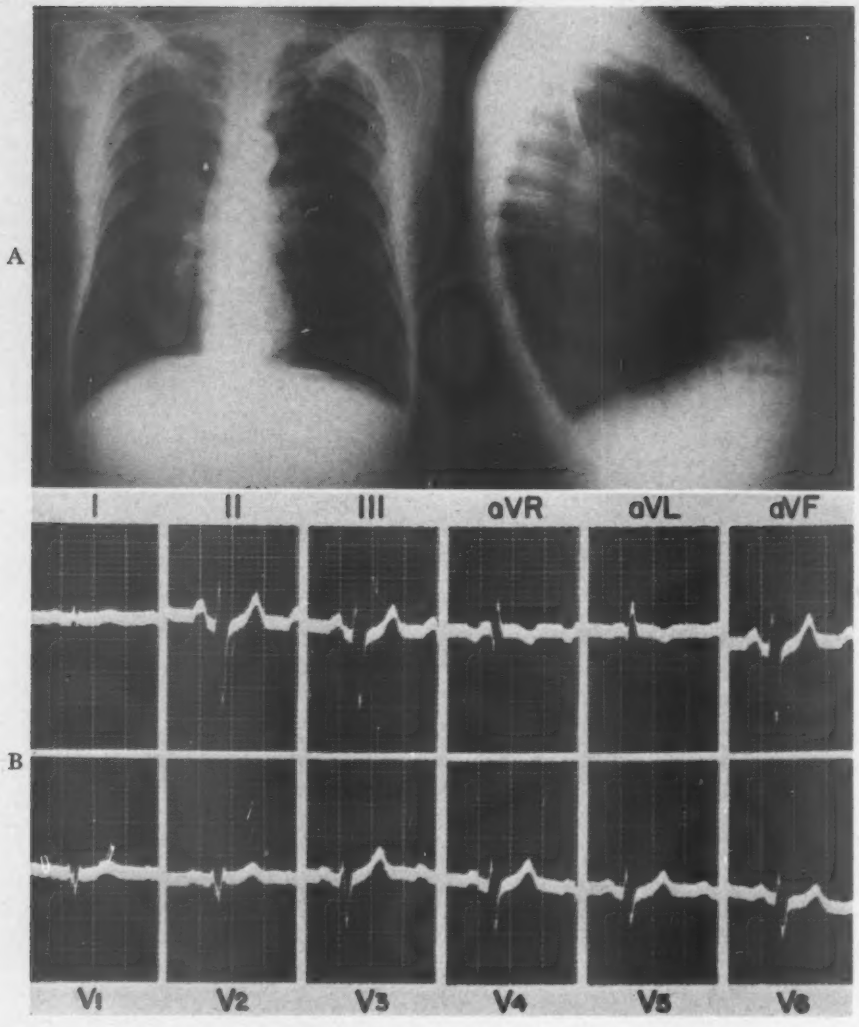


FIG. 6. Case 6. A, posteroanterior and lateral roentgenograms. B, electrocardiogram showing perpendicular QRS axis (−90 degrees).

chitis and bronchial asthma. Increasing dyspnea, duskiness and edema were noted during the last two years. There was florid congestive failure, moderate cyanosis and clubbing. The hematocrit was 61 per cent. A chest film is shown in Figure 8A.

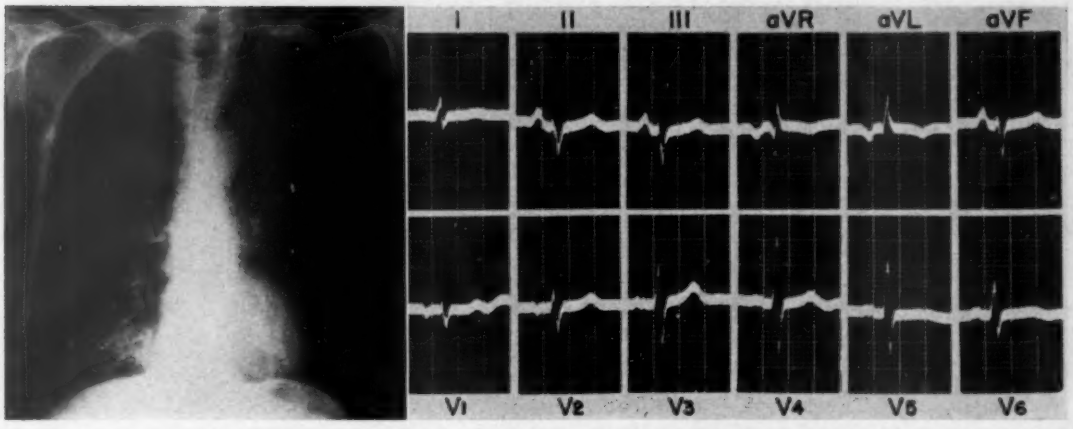
The electrocardiogram (Fig. 8B) showed normal QRS conduction with an electrical axis of −120 degrees and a P axis of +80 degrees. All precordial QRS complexes were negative and almost identical in appearance. The only positive QRS deflection was found in lead aVR.

CASE 9. A forty-seven year old man entered the hospital with a long history of chronic pulmonary infection and bronchial asthma. There was extensive deformity of the chest and pulmonary emphysema. He was in congestive failure. He died a few days after these records were obtained. Findings at autopsy included the anticipated pulmonary changes together with right ventricular dilatation and hypertrophy. There was no coronary artery disease and no myocardial infarction.

The roentgenograms (Fig. 9A) showed pulmonary emphysema and low diaphragms. The heart, although not absolutely enlarged, was probably large for the individual.

The electrocardiogram (Fig. 9B) showed relatively low voltage and an indeterminate QRS axis in the frontal plane approaching −90 degrees. There were a +90 degrees P wave axis and QS complexes with negative T waves in leads V_1 through V_3. V_4 was largely negative and also had a negative T wave. The findings resembled those of an anteroseptal myocardial infarction.

CASE 10. A fifty-five year old man (when first seen) entered the hospital with bronchial asthma, chronic bronchitis and pulmonary emphysema. In the ten-year period which followed, he was admitted to the hospital on numerous occasions for pulmonary infections and status asthmaticus, and terminally with congestive failure due to cor pulmonale. At autopsy there was extensive pulmonary emphysema, fibrosis and chronic infection. The right ventricle



A B

FIG. 7. Case 7. A, posteroanterior roentgenogram showing pulmonary emphysema. B, electrocardiogram showing vertical QRS (−90 degrees).

was dilated and hypertrophied and there was moderate coronary arteriosclerosis. However, there were no occlusions and no myocardial infarcts.

The first electrocardiogram taken in May 1948 (Fig. 10A) was representative of a number of previous records and was within normal limits. It showed a QRS axis of +90 degrees and a P axis of +60 degrees. The second record was made one month after the first during an admission for acute bronchitis (June 1948). It showed a change in electrical axis of the QRS to −90 degrees and of the P waves to +90 degrees. There was a loss of R waves in leads V_1 through V_4 and T wave inversions occurred in all the limb leads, excepting aVR which showed an abnormally upright T wave, and in all of the precordial leads. The P waves had become taller and more peaked. The findings were most similar to those attending an anteroinferior myocardial infarction. At this time, however, there were neither symptoms nor signs which could have been attributed to acute coronary artery disease.

The third electrocardiogram taken in July 1948 and obtained one month after the second (Fig. 10A) showed a QRS axis at right angles to the frontal

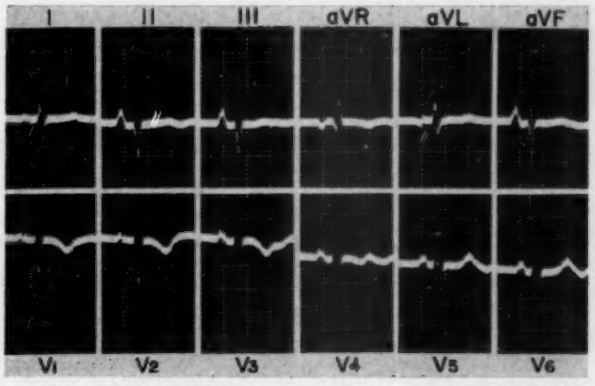
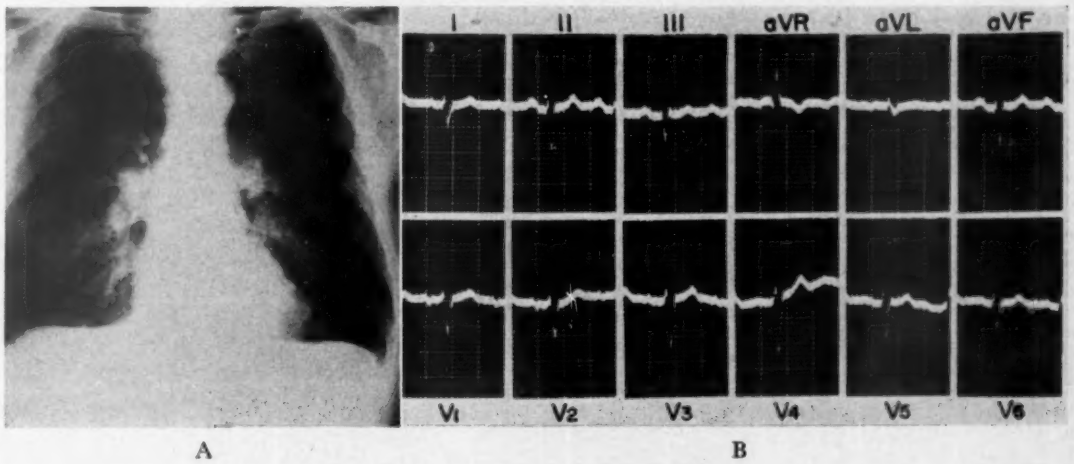


FIG. 7C. Case 7. Electrocardiogram taken five years later. Inverted T in leads V_1 through V_3 due to cor pulmonale.



A B

FIG. 8. Case 8. A, posteroanterior roentgenogram showing emphysema and cor pulmonale. B, electrocardiogram showing negative QRS in all precordial leads. QRS axis −120 degrees.

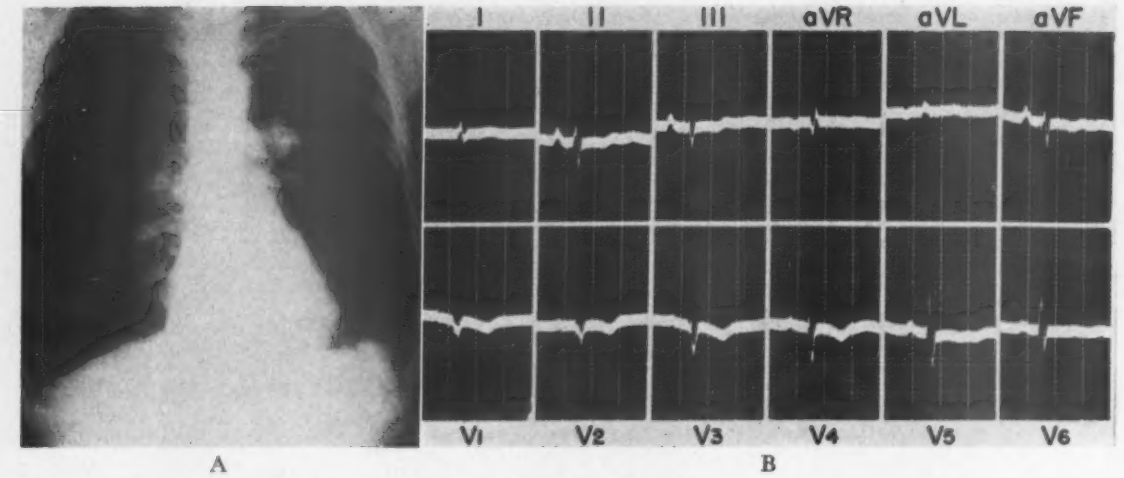


FIG. 9. Case 9. Emphysema and cor pulmonale. A, posteroanterior roentgenogram. B, electrocardiogram showing low voltage and findings simulating myocardial infarction.

plane and a P axis of +90 degrees. R waves had reappeared in the precordial leads but the abnormal T waves persisted. The findings were now more representative of right ventricular strain.

The fourth electrocardiogram taken nine months after the initial tracing (Fig. 10A, February 1949) was characteristic of the pattern of pulmonary emphysema just described. The QRS axis was perpendicular to the frontal plane of the body and prominent P waves occupied an axis of +90 degrees. The T waves were now normally upright everywhere except in leads aVR and aVL, both leads being essentially identical in appearance. All the precordial QRS complexes were negative.

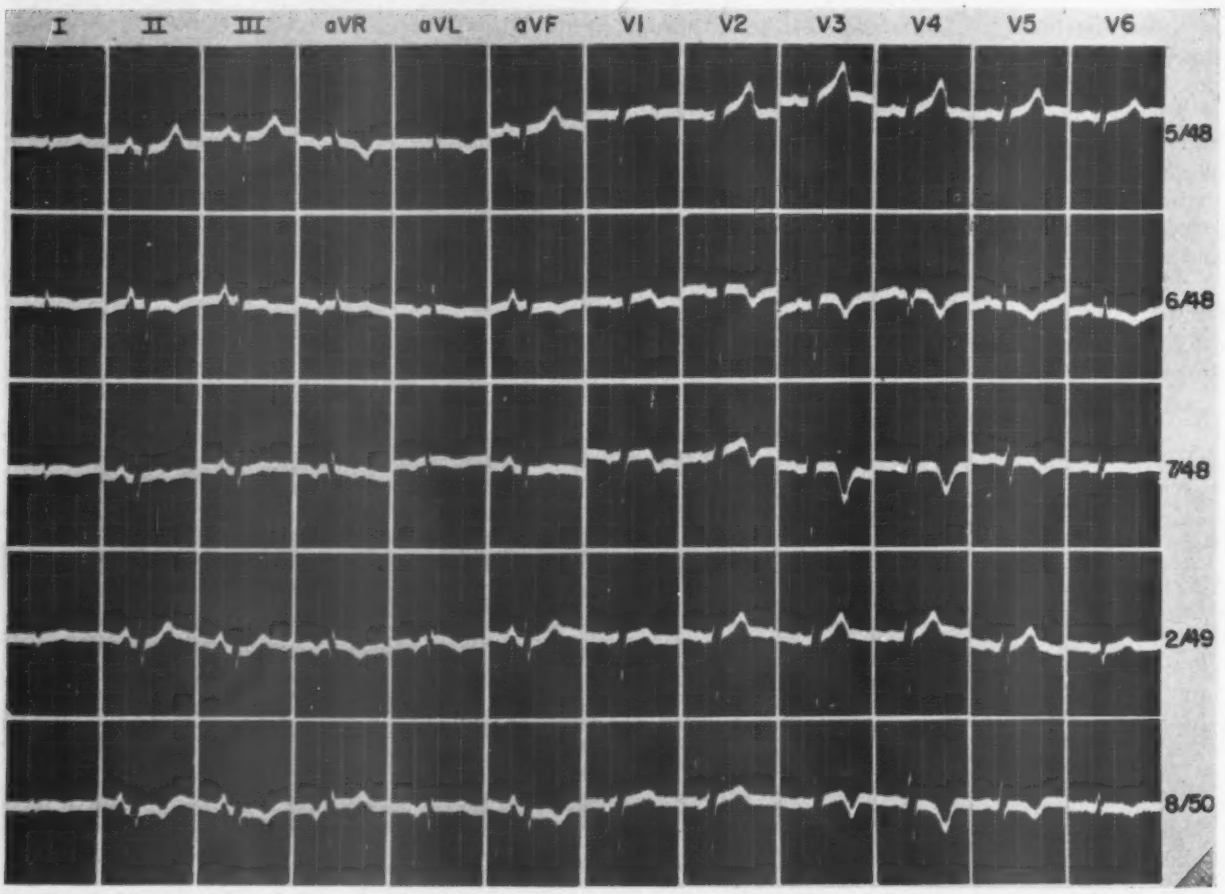


FIG. 10A. Case 10. Emphysema and cor pulmonale. Serial electrocardiograms showing changes simulating acute myocardial infarction.

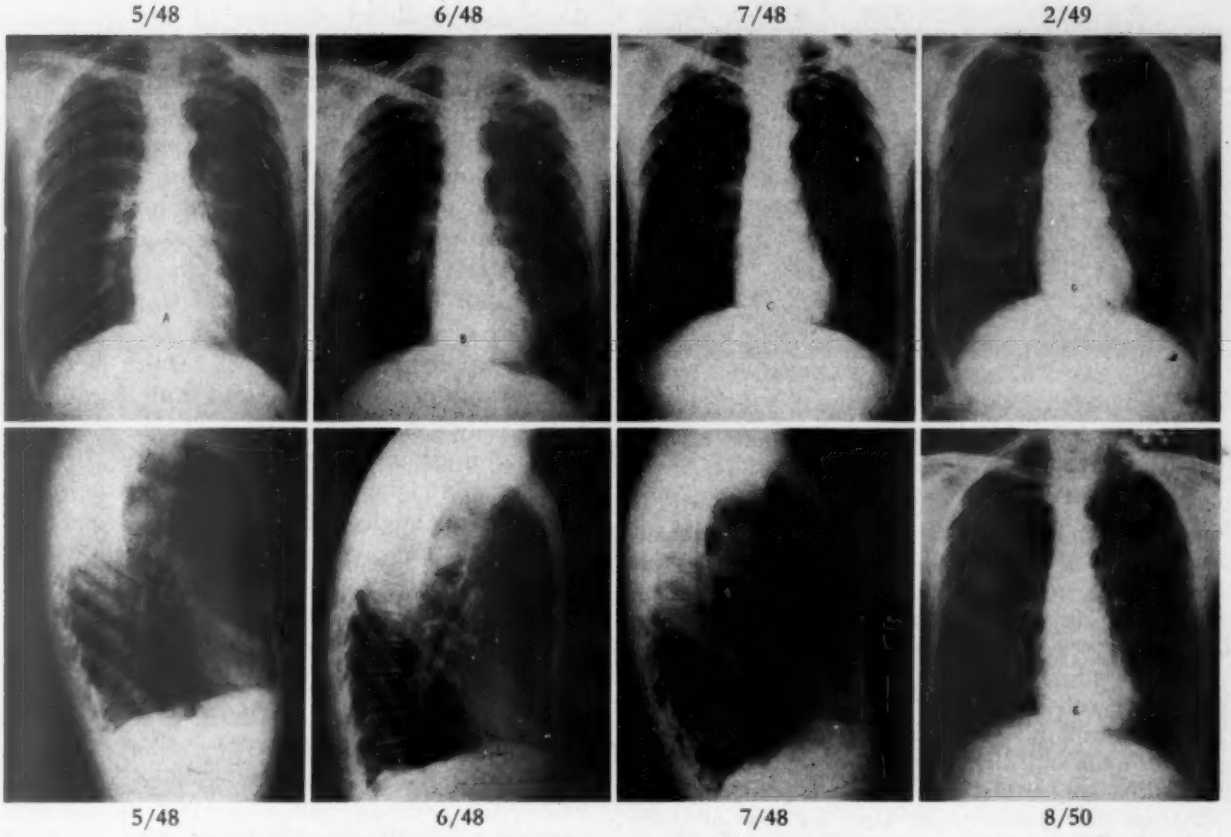


FIG. 10B. Case 10. Roentgenograms taken on same dates as in Figure 10A.

The fifth electrocardiogram made some eighteen months later (August 1950) showed redevelopment of the abnormalities seen in the third record. This, too, occurred during a bout of infectious bronchitis. Similar changes were noted on several subsequent occasions although none was quite as striking as the initial disturbance. At no time during this series of electrocardiograms did the patient have any complaints or findings suggesting primarily a cardiac origin for the observed changes. However, congestive heart failure did develop approximately two years before he died and several years after the last electrocardiogram in this series was taken.

Posteroanterior and lateral roentgenograms obtained at the same time as the electrocardiograms are shown in Figure 10B. There was little if any identifiable change in cardiac position to account for the extraordinary alteration of "electrocardiographic position."

CASE 11. This was a fifty-eight year old man with a twenty-five-year history of repeated pulmonary infections and bronchial asthma, and with evidence of fibrosis and emphysema. There was a barrel-shaped deformity of the chest, cor pulmonale and congestive failure. He died not long after the record in Figure 11 was obtained.

The electrocardiogram showed a QRS axis of approximately -120 degrees and a P wave axis of $+90$ degrees. The P waves were also abnormally tall and peaked. There was a tall R′ in lead V_1 and a deep S wave in lead V_6. The T waves were abnormally inverted in leads V_1 through V_5. The findings were those of right ventricular hypertrophy with P and QRS axes in the frontal plane which provided a clue to its origin. These were exceptional findings in pulmonary emphysema.

CASE 12. This was a sixty-seven year old man with extreme pulmonary emphysema. There was a his-

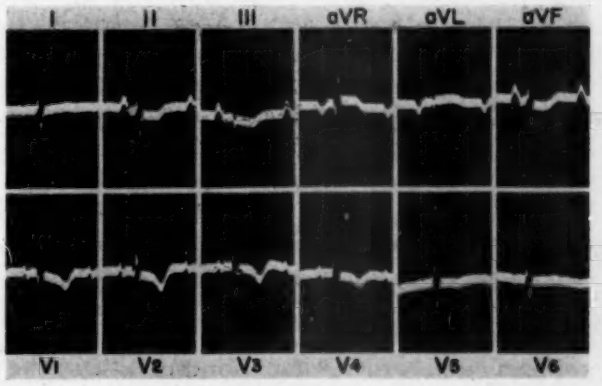


FIG. 11. Case 11. Emphysema and cor pulmonale. Electrocardiographic findings of right ventricular hypertrophy.

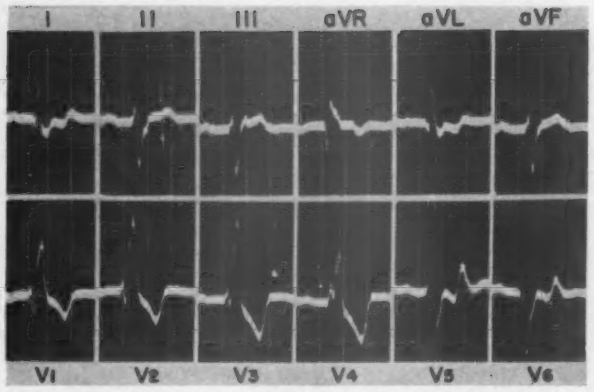


FIG. 12. Case 12. Emphysema and cor pulmonale. Electrocardiographic findings of right bundle branch block.

tory of chronic pulmonary infection and bronchial asthma dating back for many years. There was arterial oxygen unsaturation and secondary polycythemia. He was in chronic congestive failure during the last several years of his life.

The electrocardiogram (Fig. 12) showed right bundle branch block with huge R′ waves over the inner precordium. The QRS axis was approximately −60 degrees and there was first degree A-V block. Curiously, the P waves were not especially large although they exhibited an electrical axis of +80 degrees. Probably, the diagnosis of pulmonary emphysema or right ventricular hypertrophy could not be made on this record despite the right bundle branch block.

COMMENTS

Frequency of Electrocardiographic Changes: The majority, possibly 85 per cent, of all patients with emphysema of the lungs exhibit recognizable electrocardiographic aberrations. These are often found in the absence of pulmonary impairment but are almost invariably present with clinical, symptomatic disease. The earliest, most frequent and constant changes are those involving the P waves. Approximately 70 per cent of patients with emphysema will have varying but readily identifiable deviations of the QRS complexes. Electrocardiographic abnormalities, which can be confused with those of coronary heart disease, are seen in 2 to 3 per cent while the pattern of classic right ventricular hypertrophy is exceptional and is seen in no more than 5 to 8 per cent.

Factor of Cardiac Rotation and Displacement: Except for the P waves, which show relatively uniform and unvarying abnormalities, the electrocardiographic pattern of pulmonary emphysema is composed of apparently normal complexes in unusual combination. Were these the result of changes in the anatomic position of the heart, they might be explained by extensive backward displacement of the apex with or without coincidental clockwise rotation of the heart around its long axis. At best, however, this is conjectural and cannot be supported by the radiographic findings. One pattern, for example, is seen in which leads aVR, aVL and V_1 all closely resemble each other (Fig. 3). It would be difficult to conceive of any position which at the same time could expose a single aspect of the heart to both shoulders and the right anterior chest.

Nevertheless, the curious electrocardiographic findings of emphysema have, in the past, been ascribed to anatomic rotation of the heart. One such patient was a 54 year old sailor with emphysema, cor pulmonale and congestive failure.[4] It was believed, in this reported case, that the septum was oriented in the frontal plane of the body with the dilated right ventricle entirely anterior and the left ventricle posterior. In addition, retrodisplacement of the apex was postulated so that the right ventricle was also inferior and the left superior. This patient displayed an electrocardiogram with an electrical axis of −90 degrees, QS deflections in leads V_1 through V_4 and a negative complex in leads V_5 and V_6.

However, gross anatomic clockwise rotation of the heart is not susceptible to proof in the intact patient and is not seen at operation or autopsy. Backward displacement of the apex which should be readily apparent in lateral radiograms is not, in fact, observed. The altered, barrel-shaped chest often permits pulmonary herniation in front of the heart. This takes place superiorly and, if it does so at all, appears to move the great vessels backwards, the apex becoming relatively anteverted. The low, flat diaphragm which tends to restore and exaggerate the hanging position of the heart does not, however, cause retrodisplacement of the apex. A relative backward movement of the apex might occur if the frontal plane of the body were tilted backwards at the shoulders while the heart retained its original dependent position. This could follow backward migration of the shoulders upon the barrel-shaped chest. In fact, however, the arms appear to retain their central position or to move forwards on the emphysematous and kyphotic chests.

Factor of Altered Conduction Pathways: It appears rather more likely that the perpen-

dicular heart of pulmonary emphysema is more apparent than real and that the electrocardiographic position is due to distortion of the extracardiac pathways of electrical conduction rather than to anatomic rotation of the heart.[5] Although normal lung tissue has been shown to be a fairly good conductor,[6] emphysematous lung with its inflated, often bullous consistency and impoverished blood content must surely make for a great reduction in electrical conductivity. It is of some interest that somewhat similar findings have been observed in the presence of spontaneous pneumothorax with mediastinal emphysema.[7] The bulk of the cardiac electrical activity is normally conducted headwards along the great vessels, backwards through the dorsal muscles and footwards through the diaphragm. Anterior conduction through the lungs is somewhat more limited.[8,9] These pathways must be greatly altered when the heart is enveloped by emphysematous lung. Probably most of the conduction takes place cephalad through the great vessels and caudad through the diaphragm and liver. Electric potentials obtained from electrodes on the chest and limbs must arrive at these points by long and circuitous routes and almost certainly do not represent equivalents of semidirect leads.

Cause of T Wave Changes: T wave abnormalities, in the absence of right bundle branch block or the findings of classic right ventricular hypertrophy, are relatively uncommon and appear to be due either to right ventricular strain (Fig. 7C) or to apparent clockwise rotation (Fig. 3). At other times T wave inversions result in findings which suggest myocardial infarction (Figs. 9 and 10A). The pattern of classic right ventricular hypertrophy (Fig. 11) is most uncommon and is not necessarily evidence of more severe disease than that seen with the more usual electrocardiographic findings. Similarly, right bundle branch block (Fig. 12) is infrequent. Here, too, the electrocardiographic position may be obscure. Although it might be anticipated on theoretical grounds, low voltage of the QRS complexes is not often encountered (Fig. 9).

Resemblance to Myocardial Infarction: The electrocardiographic changes of chronic myocardial infarction, although variable, are actually represented by normal patterns displayed in unnatural locations. For example, the deep, wide Q followed by a negative T normally obtained from the lead in the right arm would be wholly abnormal over the apex of the heart or the left leg. In emphysema of appropriate degree an electrode over the precordium may encounter electrical events which originated at a point 180 degrees away and can, therefore, exhibit a QS complex together with a negative T wave. This form may be quite similar to that of an anterior myocardial infarction.[10,11] Similarly, in some patients with emphysema, the largely or wholly negative QRS complex in lead aVF found with an axis of −90 degrees is similar to the findings of an inferior infarction (Fig. 7C). This can occur simultaneously with loss of R waves in many of the precordial leads and can simulate an anteroinferior infarction (Fig. 10A). The T wave abnormalities which occur coincidentally are probably due to the same mechanism and merely accompany alterations of the QRS. They may, however, be primary and result from actual right ventricular strain or dilatation.

P Wave Changes: Concomitant enlargement of the P waves implies atrial dilatation but may, in part, result from change of position. If all the electrocardiographic deviations could be ascribed to altered conductivity, the P wave axis would be expected to migrate in the same direction as the QRS and to a comparable degree. Unfortunately for the theory, however, such support is lacking. P wave axes have been noted to change from +60 to +90 degrees while the QRS rotated from +90 to −90 degrees (Fig. 10A). The P wave axis is, curiously, very close to +90 degrees in almost all patients with pulmonary emphysema.

Correlation of Electrocardiographic Changes with Anatomic Right Ventricular Hypertrophy: Although the usual electrocardiographic criteria for right ventricular hypertrophy (Fig. 11) are rarely fulfilled in patients with pulmonary emphysema, patients with this disorder who come to autopsy almost always have measurable hypertrophy of the right heart. One may, therefore, infer the presence of right ventricular hypertrophy from the electrocardiographic changes of emphysema although the diagnosis of cor pulmonale must be reserved for those patients who exhibit cardiac enlargement and congestive failure.

Summary and Conclusions

Pulmonary emphysema, probably through altered extracardiac conductivity of the elec-

trical events of the heart, causes curious but readily identifiable electrocardiographic patterns. The findings suggest an extraordinary position of the heart with backward displacement of the apex and clockwise rotation. This is not, however, confirmed by x-ray examination.

Altered conduction pathways also contribute to or account for the appearance of electrocardiographic changes simulating myocardial infarction.

P wave abnormalities are noted which do not, however, lend support to either anatomic movement or pseudorotation of the heart due to disturbances of conduction.

Late but less common changes include frank right ventricular hypertrophy and right bundle branch block, frequently with obscure electrocardiographic position.

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The Vectorcardiogram in Chronic Chagas Myocarditis

An Analysis of the Intraventricular Conduction Delays Associated with a Superiorly Oriented ÂQRS*

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THE ELECTROCARDIOGRAPHIC pattern in the chronic stage of Chagas myocarditis is often highly characteristic.[1] There is evidence of a complete right bundle branch block pattern associated with a superiorly oriented ÂQRS.

Cabrera et al.[2] described a superior orientation of the ÂQRS in cases of chronic coronary insufficiency with or without associated hypertension. Similar findings were reported in congenital defects, such as persistent common atrioventricular canal[3] and Ebstein's disease.[4] In all these conditions the superior orientation of the ÂQRS is thought to be related to left ventricular overloading. Wachtel et al.,[5] analyzing the vectorcardiograms of patients of the older age group who showed a superior orientation of the QRS sÊ with a terminal delay, concluded that left ventricular hypertrophy associated with an intraventricular conduction disturbance was present.

The purpose of this paper is to analyze the vectorcardiogram in cases of chronic Chagas myocarditis in order to correlate the electrogenesis of the conduction delay with an abnormal superiorly directed ÂQRS.

MATERIAL AND METHODS

Fourteen patients with chronic Chagas myocarditis were studied. The diagnosis was suggested by clinical and epidemiologic studies, and proved in thirteen patients by the Machado-Guerreiro test. Of the total number of patients, ten were males and four females. They ranged in age from sixteen to fifty-eight years, while eleven ranged from thirty to forty-eight years of age.

The criterion for the selection of these patients was the presence of an electrocardiogram showing a QRS complex which was equal to or greater than 0.12 second in duration and was associated with a superiorly oriented ÂQRS.

The vectorcardiograms were obtained by means of the cube method of electrode placement as described by Grishman et al.,[6] the oscilloscope beam being interrupted 400 times per second. The A, B and C components were recorded simultaneously at a paper speed of 50 mm. per second, the standardization being 15 mm. = 1 mv.

RESULTS

According to the appearance of the QRS loop in the horizontal plane the vectorcardiograms were classified in three groups.

Group I: Cases 1 to 6 (Fig. 1): Characteristically, the QRS loop in the horizontal plane showed the pattern of right bundle branch block:[7] the QRS sÊ loop was inscribed counterclockwise with a delayed terminal appendage directed anteriorly and to the right. In lead V_1, the QRS complex was of the rsR′, rsr′ or R type.

In two patients in this group (Cases 1 and 2) the initial portion (0.015 second) of the QRS loop was directed forward, downward and to the right, showing a slowing in one patient. After appropriate amplification, there was evident shortening of the initial forces in

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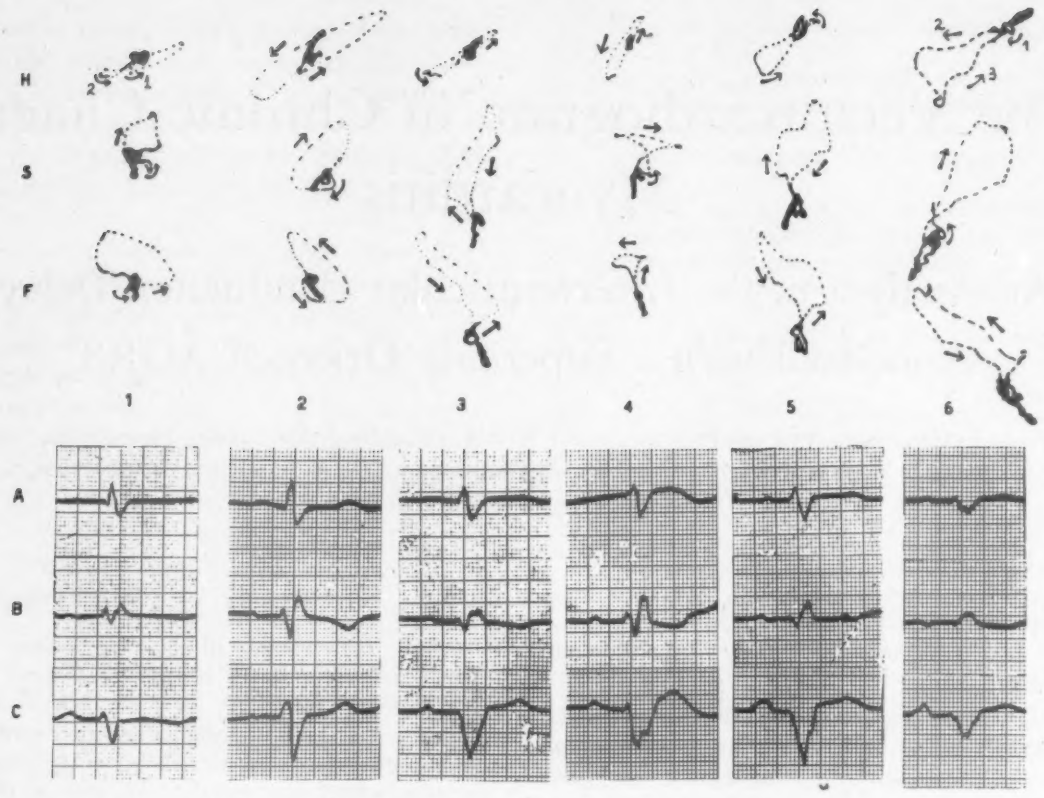

FIG. 1. Group I. Cases 1 to 6. Chagas myocarditis. Horizontal (H), sagittal (S) and frontal (F) vectorcardiographic loops above and simultaneous component A, B and C leads below. Paper speed 50 mm./second; standardization 1 mv. = 1.5 cm.

two patients (Cases 1 and 4) as compared with that seen in normal subjects and abrupt and strongly angulated first component in relation to the remaining portions of the loop. In the other three patients the initial portion was directed upward and to the left, being delayed and aberrant in one patient (Case 6).

The second portion (0.035 to 0.04 second) of the loop was directed backward and to the left and showed a decreasing amplitude from Case 1 to Case 6.

The final portion was directed forward, downward and to the right, being the predominant component in four patients (Cases 3, 4, 5 and 6). It showed a significant preterminal delay which extended to the end of the QRS in four patients (Cases 1, 2, 4 and 6) (Figs. 2 and 3).

In the frontal plane (Cases 1, 2, 3, 5 and 6) the QRS loop showed a counterclockwise inscription as well as superior orientation. In one patient (Case 4) the QRS loop assumed a figure-of-eight configuration.

The T loop spatially opposed the terminal portion of the QRS.

Group II: Cases 7 to 10 (Fig. 4): Characteristically, the QRS loop in the horizontal plane followed the pattern described by Cabrera et al.:[2] the QRS sÊ loop was inscribed predominantly clockwise in the initial portions and inscribed counterclockwise in the terminal portion with a preterminal delay. In lead V_1 the QRS complex was of the rsR′ or rsR′s′ type (Figs. 5 and 6).

In three patients (Cases 7, 9 and 10) the initial forces of the QRS loop were directed forward, downward and to the right, showing a very bizarre contour in Case 9 (Fig. 7). In one patient (Case 8) it was impossible to determine the orientation. There was a significant delay and an abrupt angulation of the first portion of the loop in two patients (Cases 7 and 8).

The second portion was directed backward, upward and to the left. In all patients the QRS loop turned forward, upward and to the right. The preterminal portion was inscribed counterclockwise. There was a definite delay in the preterminal and terminal portions of the loop in all patients.

In the frontal plane the QRS loop was inscribed predominantly counterclockwise. In two patients (Cases 7 and 9), because of a clock-

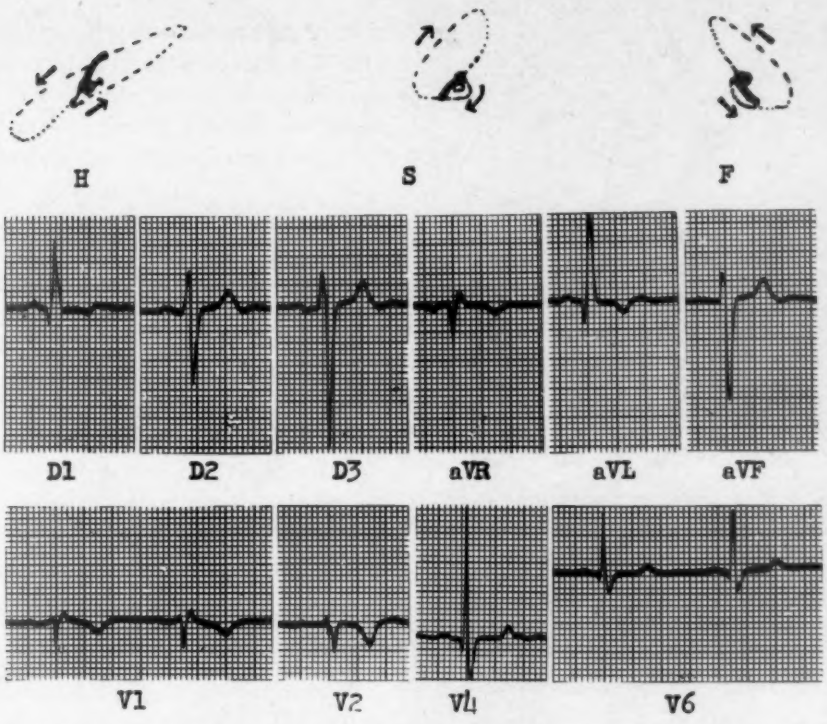

FIG. 2. Group I. Case 2. Vectorcardiogram and electrocardiogram.

wise inscription of its initial portion, the QRS loop assumed a figure-of-eight configuration.

The T loop in all patients in this group spatially opposed the terminal portion, i.e., pointed backward, downward and to the left.

Group III: Cases 11 to 14 (Fig. 8): Characteristically, the QRS loop in the horizontal plane was inscribed predominantly counterclockwise. The QRS sÊ loop was directed backward and to the left. Delays occurred frequently and in different sections of the loop. In lead V_1 the QRS complex was of the QS or rS type (Figs. 9 and 10).

The initial portion of the QRS loop in all patients was directed to the left. In three patients (Cases 11, 12 and 13) the orientation was backward. The loop contour was deeply altered showing marked anterior concavity, best illustrated in two patients (Cases 12 and 13). In all patients except one (Case 12) there was an evident delay in the aforementioned portion. In three patients (Cases 11, 12 and 13) the QRS loop had a figure-of-eight configuration in the horizontal plane.

The terminal portion in all patients was oriented backward, upward and to the right. In three patients (Cases 12, 13 and 14) a terminal and preterminal delay was displaced. A delay throughout the entire QRS loop was seen in one patient (Case 11).

The inscription of the QRS loop in its frontal projection was counterclockwise in all patients.

The T loop was directed forward, downward and to the left.

COMMENTS

Our findings in each of the three groups will be discussed separately.

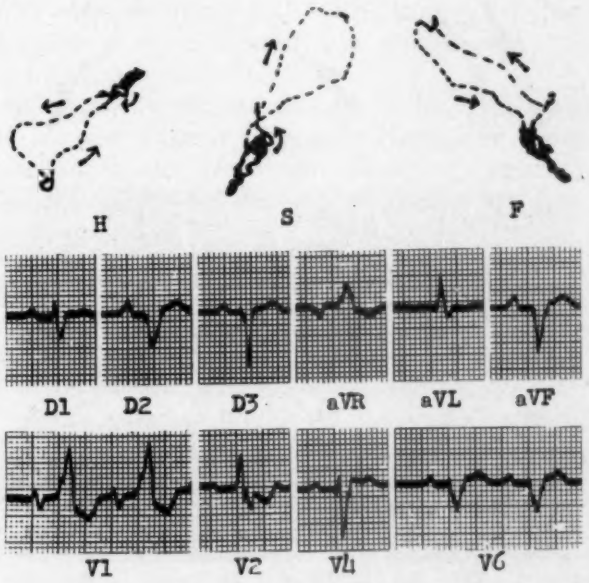

FIG. 3. Group I. Case 6. Vectorcardiogram and electrocardiogram.

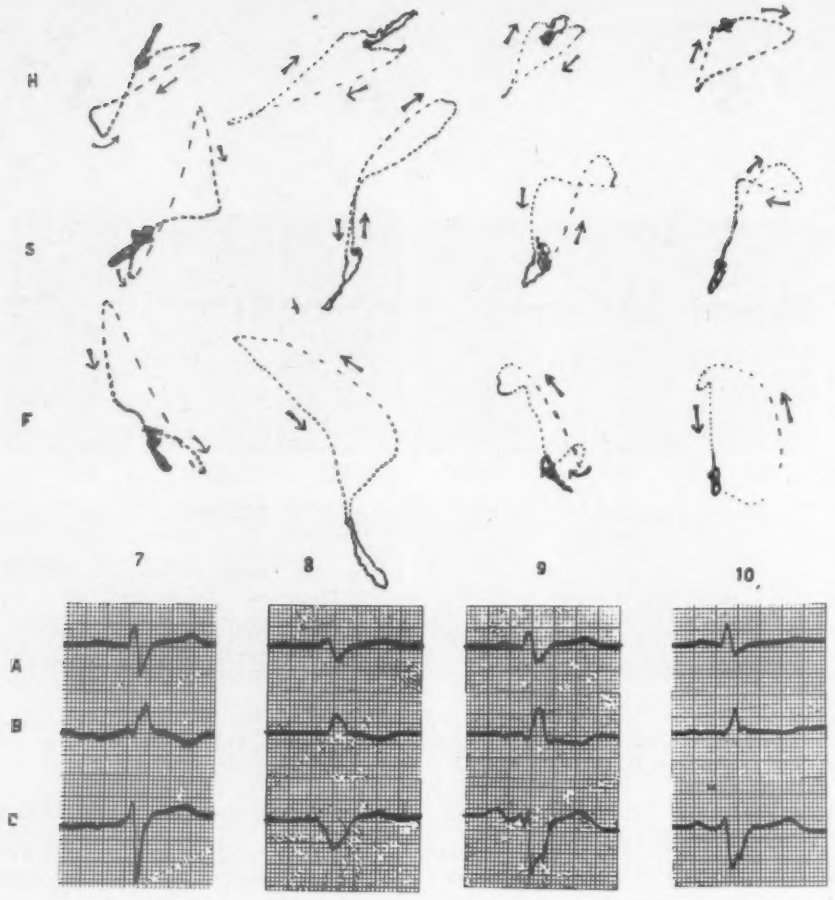

FIG. 4. Group II. Cases 7 to 10. Chagas myocarditis. Vectorcardiograms and simultaneous component leads.

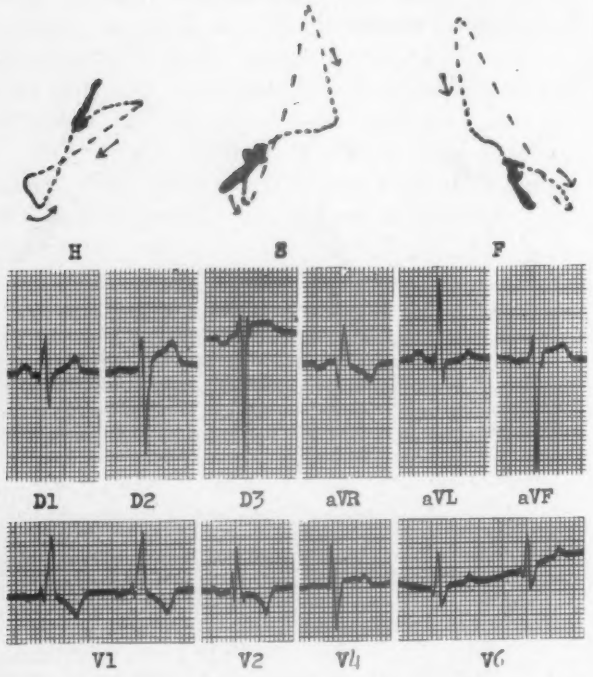

FIG. 5. Group II. Case 7. Vectorcardiogram and electrocardiogram.

GROUP I

Based upon the experimental work of Sodi-Pallares et al.[8–10] we assume that the initial forces (0.01 second) represent the activation of the medium portion of the interventricular septal mass. The abrupt angulation of the initial left component in one patient (Case 1) and the delay in another (Case 2) are probably due to septal fibrosis as found by Cabrera et al.[2] in cases of coronary sclerosis. Septal fibrosis is a common pathologic finding in chronic Chagas myocarditis.[11]

In two patients (Cases 1 and 2), the 0.025 second portion is directed to the left and backward, following the initial forces of the QRS loop, whereas in four others (Cases 3, 4, 5 and 6) this orientation is limited to the initial component of the loop. Since the activation of the apex and the left ventricular wall is reflected in the orientation of the second portion of the QRS loop, the failure of the 0.025 second portion of the loop to deviate backward and to the left in four patients (Cases 3, 4, 5 and 6) is

probably due to fibrosis and destruction of the paraseptal, apical and lateral areas of the left ventricular wall. Although we have no pathologic studies in our patients, fibrosis in these anatomic locations has been described[11,12] in cases of Chagas' disease.

In five patients in this group, delay of the terminal appendage was demonstrated. However, only one patient showed delay in the preterminal zone. This preterminal delay may be due to retardation in the passage of the stimulus from the left to the right septal ventricular mass.[8,9] The slowing throughout the entire terminal appendage suggests that there is a conduction disturbance in the right ventricular wall also. Histologic studies demonstrate an extensive subendocardial fibrosis in that ventricular wall, destroying the ramification of the Purkinje fibers.[11]

In four patients (Cases 3 to 6) there is an increasing predominance of the terminal appendage over the initial portion of the QRS loop in the horizontal projection. In one patient (Case 6) almost the entire QRS loop is formed by this terminal component. We believe that these phenomena could be explained by the destruction of the inferior and lateral portions of the left ventricle. This effect is enhanced by the presence of conduction delays in the right branch as well as in the right ventricular wall, associated with hypertrophy and/or dilatation of this chamber, described as a common finding in Chagas myocarditis.[11,12]

The T loop spatially opposes the slurred terminal portion of the QRS loop, pointing upward and to the left. In cases of laterodorsal myocardial infarction in which during the activation there is also a predominance of the electrical forces pointing anteriorly and to the right, the T sÊ loop has the same orientation of these forces.[13]

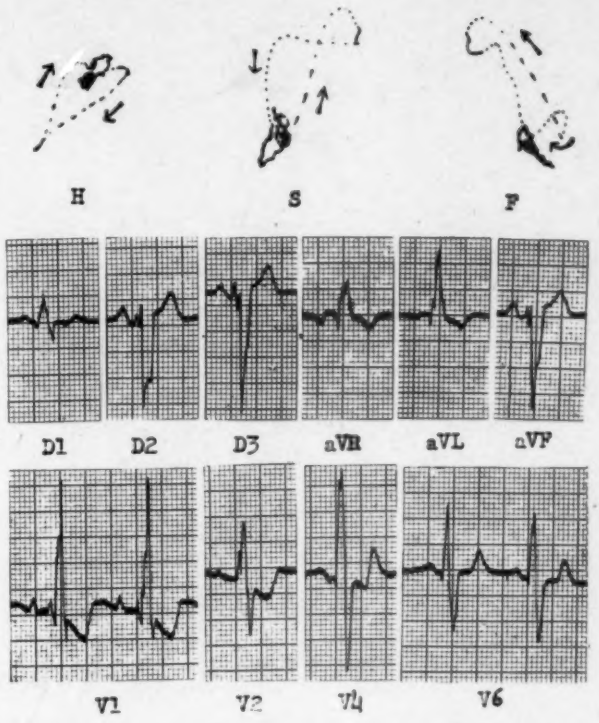

FIG. 6. Group II. Case 9. Vectorcardiogram and electrocardiogram.

GROUP II

In three patients (Cases 7, 9 and 10) the first portion of the QRS loop is directed downward, forward and to the right. This is in accordance with the orientation of the initial forces of the QRS in right bundle branch block that are related to the activation of the left septal mass.[8–10] Slowing and deformity of the initial component of the QRS loop, probably because of septal fibrosis, was seen in two patients (Cases 7 and 9).

Comparing the second part of the QRS loop in chronic Chagas myocarditis with the same portion in the vectorcardiogram of coronary insufficiency[2] we observe that in most cases of

FIG. 7. Case 9. Amplified initial portions of the QRS loop.

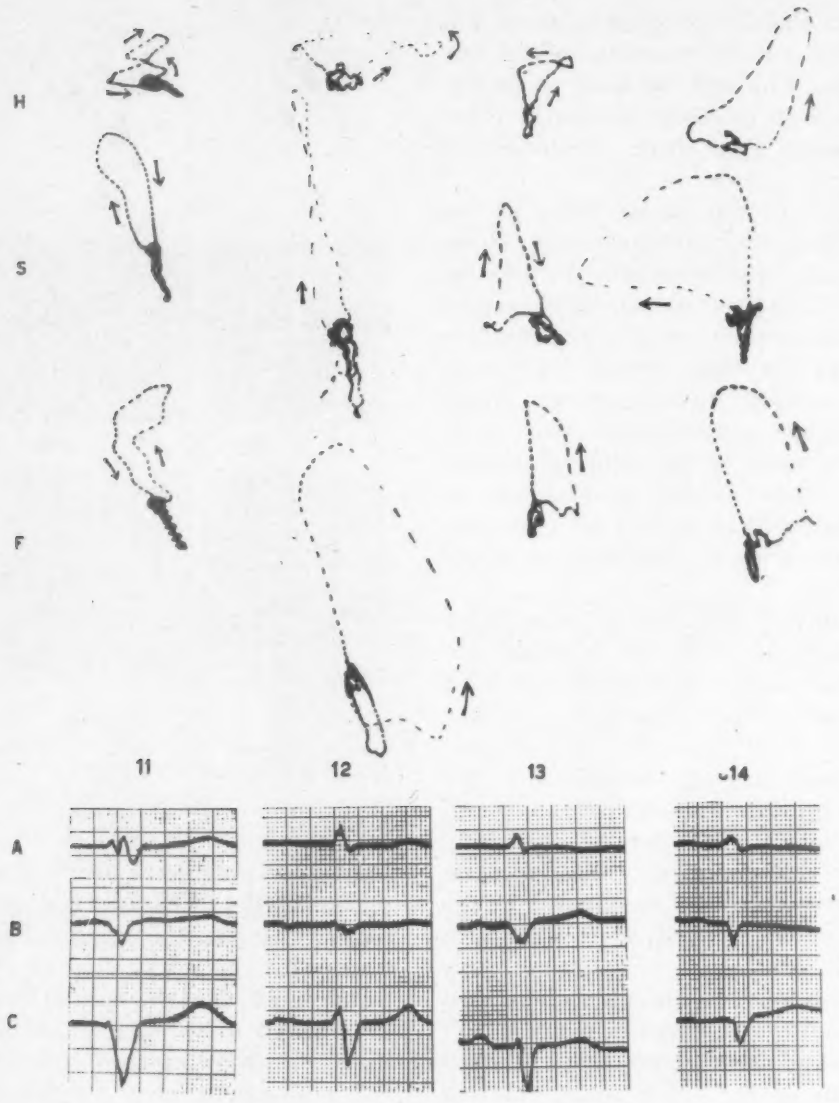

FIG. 8. Group III. Cases 11 to 14. Chagas myocarditis. Vectorcardiograms and simultaneous component leads.

Chagas' disease that component of the loop is of decreased amplitude and frequently shows slurring. These differences can be explained by the presence of more extensive fibrosis in chronic Chagas myocarditis.

The preterminal portion of the loop is directed forward, upward and to the right and shows delay and counterclockwise inscription in all patients, and its amplitude decreases from Case 7 to Case 10. In the last two this preterminal delay is of very small magnitude in the horizontal plane, resembling the loop registered in patients with marked right ventricular hypertrophy.[14] As in the first group, we believe that the preterminal and the terminal delays present in these patients are due to a conduction disturbance in the septal mass and right ventricular wall, respectively.

It is interesting to point out that the inscription is always counterclockwise in the frontal plane in all patients of this group. The upward and leftward displacement of the loop is greater than that seen in patients with coronary sclerosis who show clockwise or counterclockwise inscription in the frontal plane.[2] When associated with arterial hypertension the upward and leftward orientation is more marked. We can assume that the orientation and the displacement of the QRS loop in the frontal plane are probably related to the great enlargement of the left ventricle frequently found in Chagas' disease.

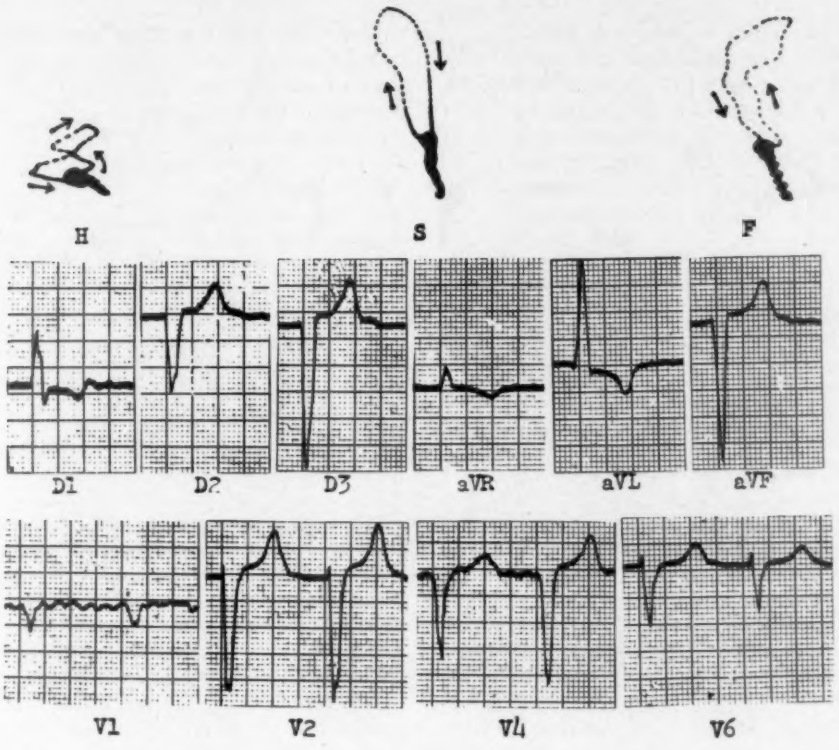

FIG. 9. Group III. Case 11. Vectorcardiogram and electrocardiogram.

In our opinion, the vectorcardiograms of the first and second groups of chronic Chagas myocarditis represent true complete right bundle branch block associated with localized delays and shortening of some portions of the loop related to areas of myocardial fibrosis. The location of this fibrosis and the left ventricular enlargement can explain the marked displacement of the loop leftward and upward.

GROUP III

Patients in this group do not show characteristics of right bundle branch block. Left ventricular hypertrophy or left bundle branch block was diagnosed from electrocardiographic interpretation in all patients. However, the vectorcardiogram showing counterclockwise inscription in the horizontal plane and delay predominantly located in the terminal portion of the loop does not support the diagnosis of left bundle branch block.

The initial portion shows delay and a bizarre contour in all patients. It is always directed to the left and in three patients points posteriorly also. These alterations can be explained by the marked fibrosis of the inferior two-thirds of the septal mass. The initial component resembles that found in cases of anteroseptal myocardial infarction.

The preterminal and terminal delay registered in three patients (Cases 11, 12 and 13) and its backward orientation suggest an intraventricular conduction disturbance probably located at the junction of the Purkinje fibers and the myocardium. One patient (Case 11) with a delay throughout the entire QRS loop reinforces this thought which can be related to the subendocardial fibrosis found in chronic Chagas myocarditis.[11]

The upward and leftward displacement of the QRS loop in this group can also be explained by the destruction of the myocardial mass and by the great enlargement of the left ventricle.

SUMMARY

Fourteen patients with chronic Chagas myocarditis showing intraventricular conduction disturbance in the electrocardiogram were studied vectorcardiographically.

According to the appearance of the QRS loop in the horizontal plane the vectorcardiograms were classified into three groups. In ten patients (groups I and II) the electrocardiographic diagnosis of a complete right bundle branch block was confirmed by the vectorcardiogram. In group I the QRS loop in the horizontal plane characteristically fol-

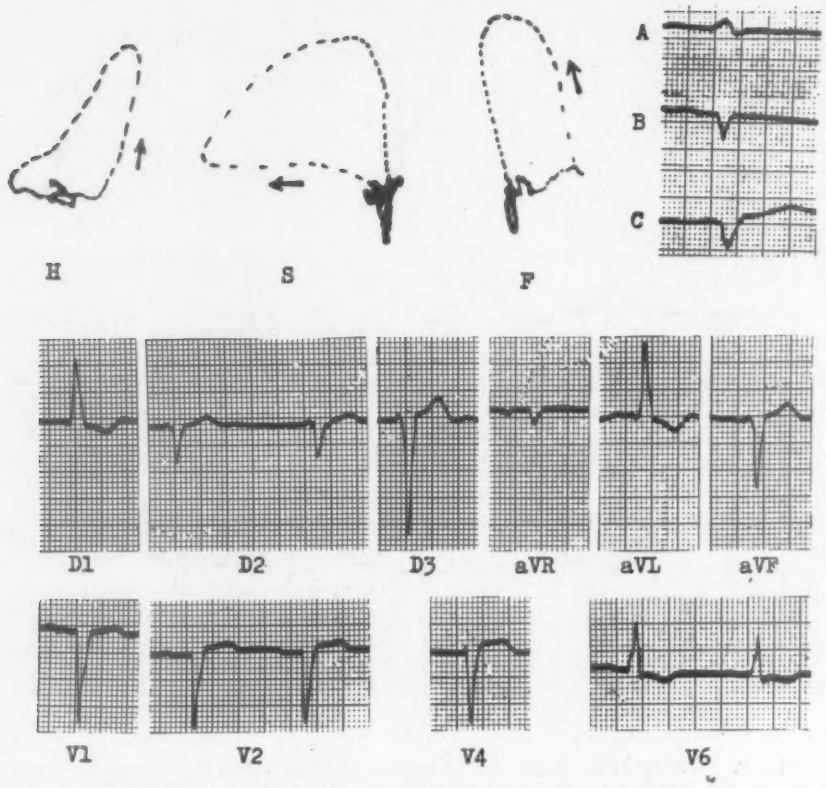

FIG. 10. Group III. Case 14. Vectorcardiogram, component leads and electrocardiogram.

lowed the pattern described by Grishman et al. for right bundle branch block. In group II the QRS loop followed the pattern described by Cabrera et al. for right bundle branch block in coronary sclerosis. In both groups, however, the vectorcardiograms brought out some peculiarities that were not given by electrocardiographic analysis, namely: (1) intraventricular conduction disturbance, probably located at the level of the connections of the Purkinje fibers with the myocardium, and (2) loss of electrical forces due to myocardial fibrosis probably located in the inferior two-thirds of the interventricular septum and free wall of the left ventricle.

The third group did not present electrical characteristics of right bundle branch block. There were signs of left ventricular hypertrophy in all four patients of this group, of whom two had been diagnosed electrocardiographically as having left bundle branch block.

The vectorcardiographic study of these patients revealed very important facts not shown by the electrocardiogram: (1) the left bundle branch block was not confirmed since the horizontal plane inscription of the QRS loop was counterclockwise in all patients and the delay was predominantly located in the terminal portion of the loop; (2) intraventricular conduction disturbances with delay in one or more portions of the loop were present in all patients; and (3) the QRS loop suggested that some electrical forces had been subtracted probably because of destruction of the myocardial tissue mainly located in the inferior two-thirds of the septum and adjacent ventricular wall.

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Experimental Study

A New Approach for the Recognition of Ventricular Premature Beats*

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THE MORPHOLOGY of ectopic beats universally recognized as of ventricular origin is similar to the patterns seen in incomplete or complete right and left bundle branch block. It would be desirable to review these patterns before presenting our findings on the morphology of ventricular ectopic beats.

In *left bundle branch block* three different patterns according to the degree of block have been observed.[1] In the first degree, the activation process descending through the left branch has a slight delay (0.01 to 0.02 second) but continues to control the depolarization of the left septal mass as well as that of the free wall of the left ventricle. The Q wave disappears and an initial slurring of the R wave is inscribed in those leads that reflect the potential variations† of the left ventricle (leads V_5, V_6, I and aVL in electrically horizontal hearts; and leads V_5, V_6, II, III and aVF in electrically vertical hearts). Figure 1B is an example of the most common morphology seen in first degree left bundle branch block.

In the second degree, the delay of the impulse in descending through the left branch reaches 0.03, 0.04 or 0.05 second. The same impulse controls the depolarization of the free wall of the left ventricle and a portion of the left septal mass. The activation which descends through the right branch depolarizes the lower septal portions belonging to the right ventricle and "jumps" the barrier that separates the opposite ventricle so as to meet with the impulse descending through the left branch in the depth of the left septal mass. Second degree left bundle branch block is recognized by a wider QRS complex with more aberrancy than in the first degree in the leads reflecting the potential variations of the left ventricle: slurrings are present in both ascending and descending branches of the R wave, there is no Q wave and the T wave is negative of the secondary type (Fig. 1C).

The delay of the impulse in the third degree of left bundle branch block is total or subtotal. The activation wave coming down through the right branch controls all or almost all the depolarization of the left septal mass and of the free wall of the left ventricle, after "jumping" the intraseptal barrier. The pattern of this type of block, called "complete," is already known (Fig. 1D).

In incomplete and complete *right bundle branch block* there are no experimental data to determine the precise moment of the "jump" effected by the activation wave from the left to the right ventricle.[1] This is the reason why we are unable to catalogue it into degrees as in left bundle branch block; however, transitional morphologies have been described making it possible to recognize complete and incomplete right bundle branch block.

Figure 2 shows the unipolar morphologies in lead V_1 with progressive degrees of right bundle branch block. As the degree of block is more advanced, the notch in the upstroke of the S wave progressively becomes a late R wave; at the same time this R wave increases in voltage and becomes more slurred. The negative displacement of the RS-T segment and the negativity of the T wave are more accentuated

† This term must not be confused with action potential.

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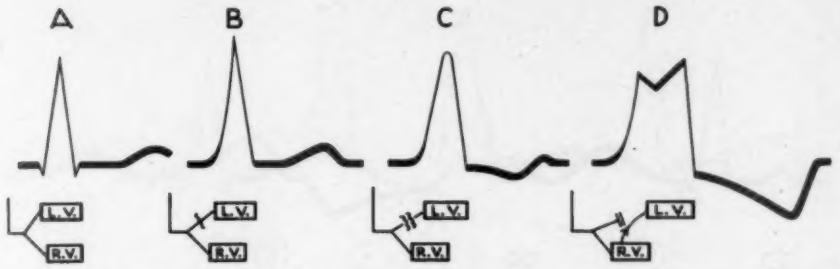

FIG. 1. Morphologies of left bundle branch block in precordial leads V_5 and V_6. A, normal electrocardiogram. B, C and D correspond to different degrees of left bundle branch block (from first to third degree). The diagrams at the bottom represent the asynchronism of ventricular activation which is greater as the degree of block advances. L.V. = left ventricle. R.V. = right ventricle.

as the block advances (secondary changes).

Right ventricular extrasystoles are those that have left bundle branch block morphologies, while left ventricular extrasystoles have patterns similar to right bundle branch block.

Most authors are in agreement with these concepts; yet we differ. The new ideas presented in this paper are based on experimental work performed on thirty dogs.

MATERIAL AND METHOD

The ectopic beats of a considerable number of electrocardiograms were studied and classified into groups. This was carried out in accordance with the morphology of the extrasystolic complex and its relation to the P wave.

The extrasystolic patterns observed in the clinical tracings were reproduced in thirty dogs. The dogs were anesthetized with sodium pentobarbital (30 mg. per kg.) and the heart was widely exposed with the usual technic. The Sanborn Poly-Viso was used for recording.

The sinus node was destroyed with a hemostat and an artificial auricular pacemaker was produced electrically with a Grass Stimulator Model S 4B in a place located near the sinus node, at a rate between 100 to 120 per minute with stimuli of 6 volts and 1 msec. in duration.

Another stimulator, coupled to the first one, was also used in order to provoke premature beats at a considerable number of points on the epicardial surface of both ventricles, on the septal surfaces, in the depth of the cardiac muscle, in the auricles and in the A-V node. The ectopic stimulus was applied every 50 msec. (between the ascending limb of T and the beginning of QRS, including the P wave and the P-R segment). The same type of experiment was accomplished in some animals in whom right or left bundle branch block was previously produced. In another dog the extrasystolic beats were produced after destruction of the A-V node.

We also studied the similarity between the extrasystoles observed in the clinical tracings and those obtained experimentally.

RESULTS

EXTRASYSTOLES WITH MORPHOLOGY OF INCOMPLETE RIGHT OR LEFT BUNDLE BRANCH BLOCK

These extrasystolic morphologies are obtained through any of the following conditions:

(*1*) *Ventricular Extrasystoles Produced Between the Peak of P (or Just Before) and the Beginning of QRS:* Ventricular extrasystoles have a morphology of incomplete bundle branch block if the ectopic impulse arises at a point in the cardiac cycle between the ascending limb of P and the beginning of the QRS complex. The

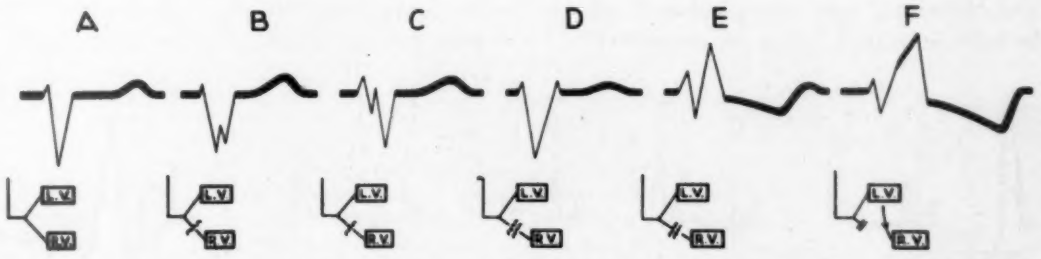

FIG. 2. Morphologies of right bundle branch block in lead V_1. A, normal electrocardiogram. B to E correspond to different degrees of incomplete right bundle branch block. F, the pattern of complete right bundle branch block. Note that the asynchronism in ventricular activation increases as the block is more advanced.

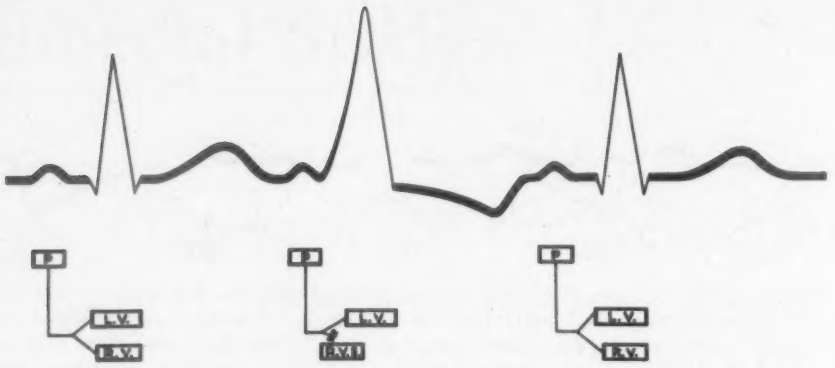

FIG. 3. Right ventricular extrasystole (R.V.E.) produced at the end of the P wave. The morphology of the premature beat is similar to that seen in second degree left bundle branch block and in Wolff-Parkinson-White syndrome. The normal sinus supraventricular wave activates the left ventricle, while the ventricular premature beat depolarizes the right.

aberrancy of QRS decreases as the ectopic stimulus discharges farther from the preceding P wave and the morphology of incomplete bundle branch block will come closer to normal.

Figure 3 shows a right ventricular extrasystole produced between the peak of the P wave and the beginning of QRS. The morphology of the premature beat is very similar to that seen in Wolff-Parkinson-White syndrome; in addition, the ventricular complex is near the P wave (short P-R interval) and the P-S interval is the same as that of the sinus complexes.

Figure 4 shows the same results obtained experimentally; i.e., as the ectopic ventricular stimulus discharges farther from the preceding P wave, the aberrancy of QRS morphology diminishes.

When the ventricular premature beat is located in this part of the cardiac cycle, a summation stimulus is produced by the following effects: (1) the normal supraventricular activation wave descending through the branch of the ventricle not stimulated, and (2) the ectopic stimulus applied in the opposite ventricle. Both ventricles are activated with slight asynchronism and morphologies of incomplete bundle branch block are recorded.[2]

(2) *Supraventricular (Atrial, or Nodal) Extrasystoles Occurring Early in Diastole:* When a premature ectopic stimulus originates in the auricular muscle or in the A-V node, the QRS complex is normal and has the same morphology as that seen in the complexes of sinus origin.

If the extrasystolic beat is inscribed early in the diastolic phase of the cardiac cycle (the P wave is superimposed on the preceding T wave), there is aberrancy of the QRS complex and its morphology is that of incomplete bundle branch block, first or second degree (Fig. 5). One can compare the morphology of the extrasystole shown in Figure 5 with that of incomplete left bundle branch block in Figure 1. In the sequence of ventricular activation schematically represented at the bottom of the figure the activation of the left ventricle is accomplished after that of the right; this is due to a delay in the recovery of the left bundle branch. Supraventricular extrasystoles with morphologies of incomplete right bundle branch block can also be observed.

In the upper row of Figure 6 three different types of supraventricular premature beats observed clinically are illustrated. In (A) the morphology of the extrasystolic complex is very similar to that of the sinus beat; in (B)

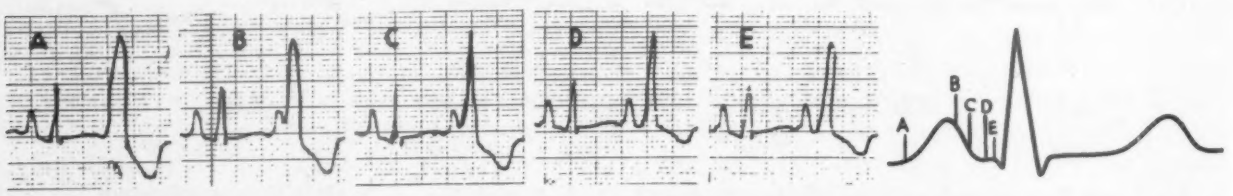

FIG. 4. Experimental ventricular premature beats in lead II produced at different places on the P-R interval. As the ectopic ventricular stimulus discharges farther from the preceding P wave, the aberrancy of QRS morphology diminishes.

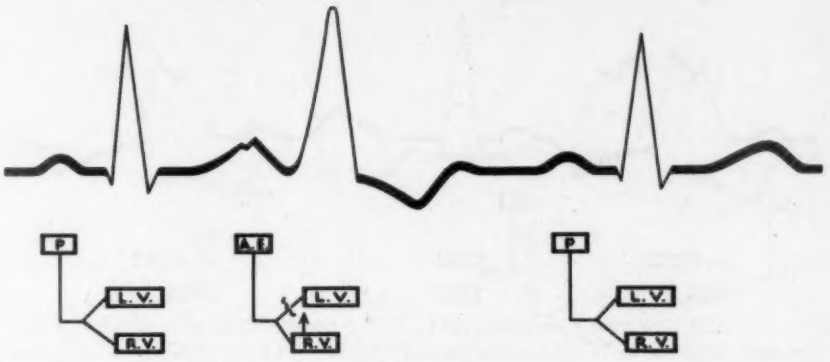

FIG. 5. Auricular extrasystole (A.E.) produced at the peak of the T wave. The ventricular complex has a morphology of second degree left bundle branch block due to the incomplete recovery of the left branch when the ectopic beat discharges prematurely.

the extrasystolic morphology is of the type of incomplete left bundle branch block shown in Figure 1; in (C) the tracing shows two consecutive premature beats that we consider of auricular origin. In the lower row of Figure 6 we have experimentally reproduced the same morphologies that are seen in the upper row, using electrical atrial stimulation. It is important to emphasize that the two consecutive auricular premature beats presented in (C) of the lower row were obtained by a *single* electrical stimulus applied in the atrial tissue near the A-V node. We cannot explain the origin of the second beat unless a re-entry phenomenon accounted for this.

(*3*) *Ventricular Extrasystoles Produced Between the Peak of P and the Beginning of QRS in the Presence of Bundle Branch Block, with Impulses Originating in the Ventricle of the Blocked Side:* In the presence of right or left bundle branch block, a ventricular extrasystole is expected to behave in the same manner as ventricular extrasystoles in the absence of bundle branch block. We are confronted with the above on many occasions (Figure 15), due to the appearance of ventricular extrasystoles early in ventricular diastole. However, we have observed that when the stimulus originates on the same side as the block (left ventricle in presence of left bundle branch block; right ventricle in presence of right bundle branch block) and located between the ascending limb of P and the beginning of QRS, the extrasystolic ventricular complexes become narrower and less bizarre as the ectopic stimulus discharges in the P-R segment closer to the QRS complex of sinus

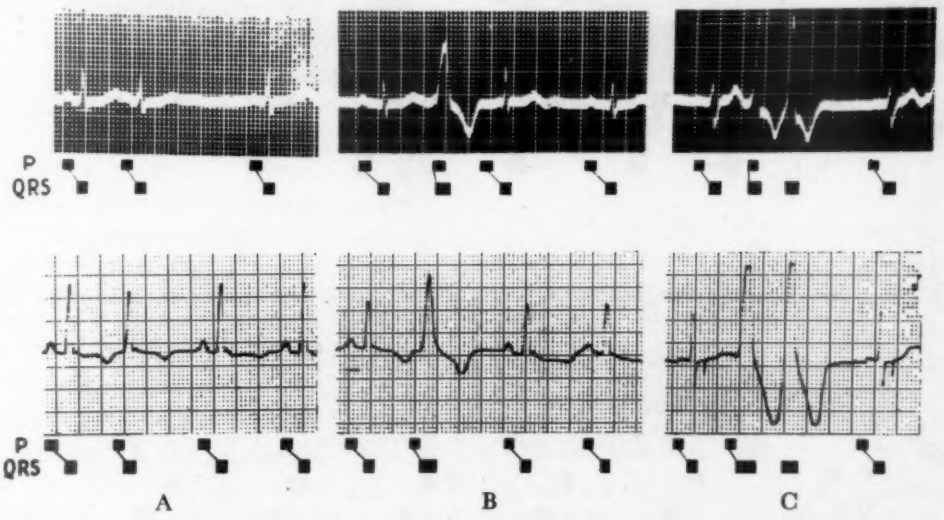

FIG. 6. Different aberrant morphologies obtained in supraventricular premature beats. The upper row shows clinical tracings while those presented in the lower row were experimentally reproduced.

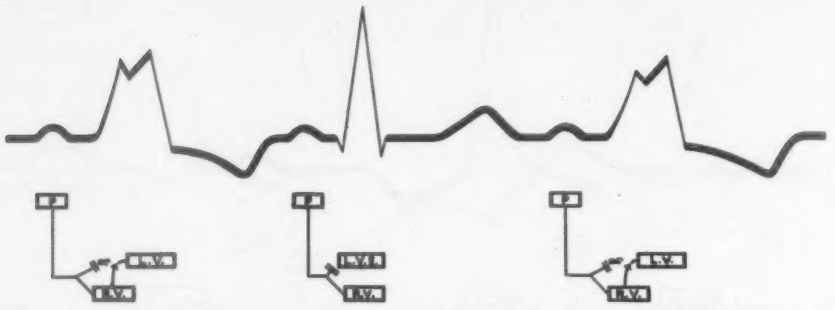

FIG. 7. Left ventricular extrasystole (L.V.E.) produced at a "critical moment" (see text) in presence of left bundle branch block. The morphology of the ectopic beat is normal.

origin. Then, the morphologies are either normal or similar to those of incomplete bundle branch block (Fig. 7).

The ventricular ectopic stimulus must arise at a "critical moment" on the P-R segment in order to produce a QRS of normal duration and morphology; this "critical moment" varies from case to case, as we have demonstrated experimentally in animals. Probably, this normal QRS duration is due to the anticipated activation of the blocked ventricle by the premature ectopic stimulus. For example, in left bundle branch block, the activation of the right ventricle is accomplished before that of the left ventricle, resulting in asynchronism of ventricular activation. A premature beat originating in the left ventricle anticipates its activation and counterbalances the effect of the block, causing a diminution or disappearance of ventricular asynchronism.

If the ectopic stimulus discharges before or after the aforementioned "critical moment," morphologies of incomplete right or left bundle branch block will be obtained, depending on the type of block existing during the sinus rhythm. If the stimulus is applied to the left ventricle before the "critical moment" in the presence of left bundle branch block, a morphology of incomplete right bundle branch block will be produced. If the stimulus is applied after the "critical moment" but before the beginning of QRS, the morphology will resemble incomplete left bundle branch block.

If there is right bundle branch block a

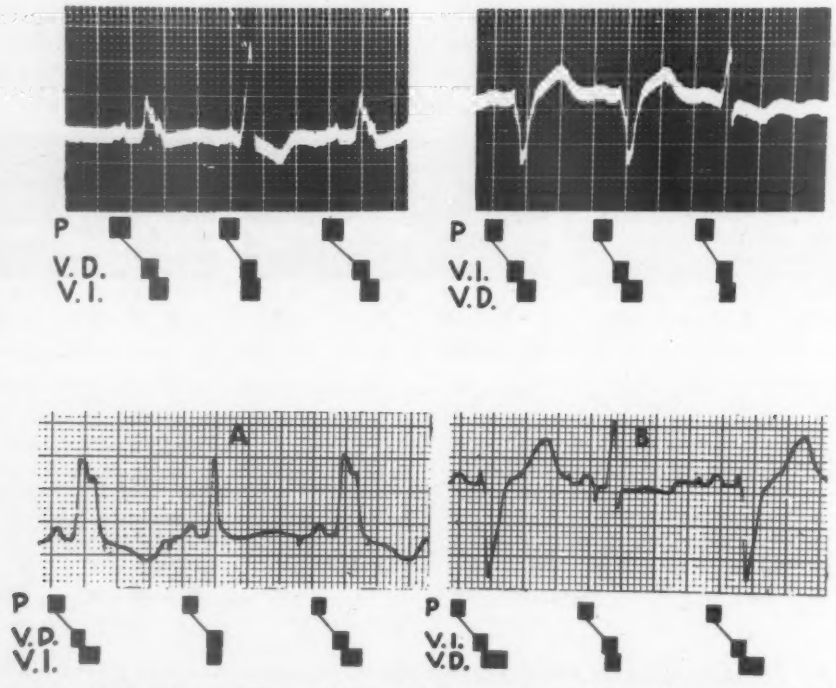

FIG. 8. Ventricular premature beats with normal duration and morphology of QRS. See text.

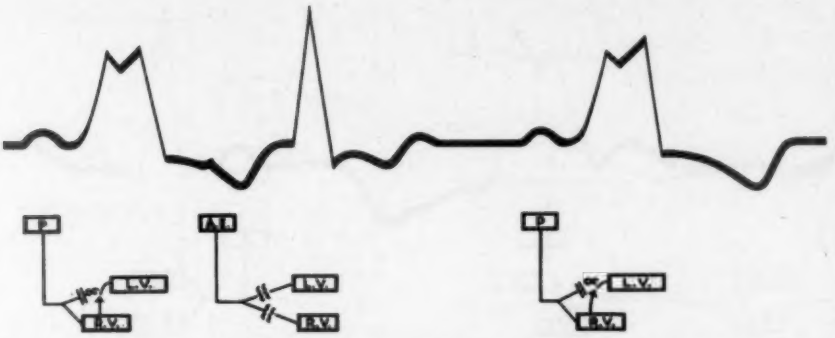

FIG. 9. Auricular extrasystole (A.E.) produced at the beginning of the T wave in the presence of complete left bundle branch block. The extrasystole has a morphology close to normal with almost synchronous activation of both ventricles. See text.

stimulus discharging before the "critical moment" will produce a pattern of incomplete left bundle branch block. However, a morphology of incomplete right bundle branch block will be produced if the ectopic stimulus is applied after the "critical moment."

In the lower row of Figure 8 two experimental ventricular premature beats of the type we are studying are presented. In (A) there is complete left bundle branch block and an ectopic stimulus (second beat) was applied at the epicardial surface of the left ventricle of a dog, a short while after the P wave. The ventricular extrasystolic complex exhibits normal morphology and duration. In (B) there is right bundle branch block and the ventricular premature beat was experimentally originated in the right ventricle. Note the same normal morphology and duration of the ventricular premature beat. In the upper row of Figure 8, similar ventricular premature beats observed in clinical tracings are presented. These cases correspond to ventricular extrasystoles with normal or slightly altered QRS complexes and with a duration below 0.10 second.

(*4*) *Supraventricular Extrasystoles (Between T and P) in the Presence of Incomplete or Complete Bundle Branch Block:* If a supraventricular extrasystole is produced in the presence of incomplete or complete right or left bundle branch block, the extrasystolic QRS complex is similar to those of sinus origin. However, we have observed experimentally that if the premature supraventricular stimulus is applied early in the diastolic phase of the cardiac cycle, the morphology of the premature beat will either approach or become normal (Fig. 9). We have observed similar tracings in a few cardiac patients (Fig. 10). This indicates a diminution in the ventricular asynchronism produced by the block.

The possible explanation of the mechanism making the ventricular complexes normal is that the unblocked branch is in a relatively refractory state when the ectopic stimulus is prematurely discharged following a short diastolic pause not sufficient for complete recovery of the branch. This explanation leads us to believe that the bundle branch continues to transmit impulses even in the presence of an advanced degree of block. Corroborating this point of view is the difficulty in provoking total bundle branch block even by experimental methods. Summarizing, both ventricles have a similar delay and there is less asynchronism of

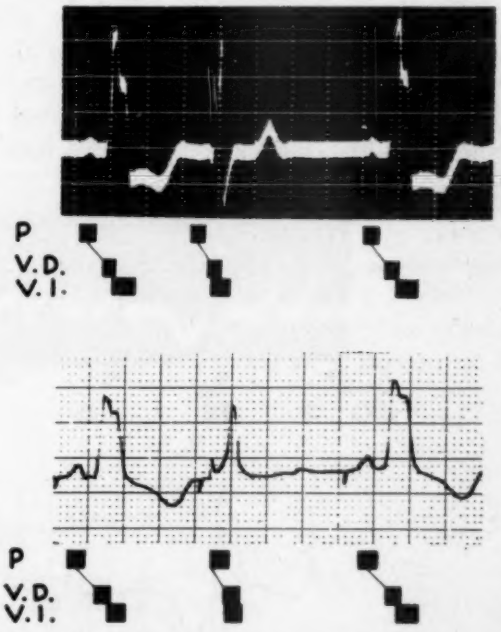

FIG. 10 Auricular premature beats in the presence of complete left bundle branch block. The lower row shows an auricular extrasystole produced experimentally in the dog's heart after the left branch was severed. In the upper row a similar premature beat of a clinical tracing is shown.

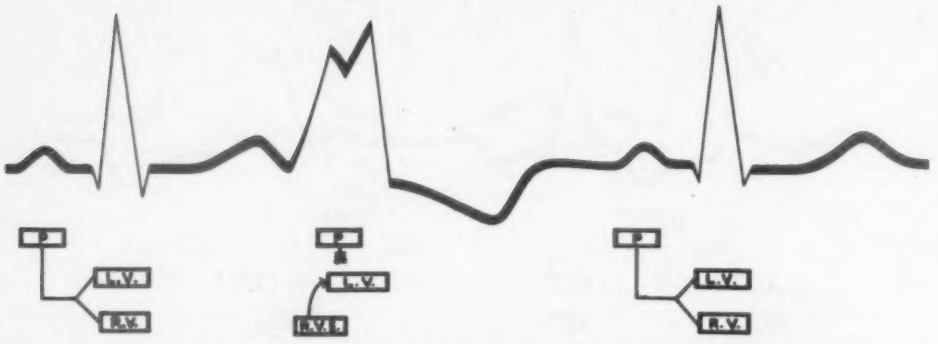

FIG. 11. Right ventricular extrasystole (R.V.E.) produced between T and P. The morphology of the ectopic beat is similar to that of complete left bundle branch block.

ventricular activation. This is the reason why the aberrancy of QRS diminishes or disappears.

Considering the four previous subgroups we may conclude that there are many ventricular extrasystoles with low ventricular aberrancy (morphologies of incomplete right or left bundle branch block and with QRS duration below 0.10 second (see first and third subgroups).

EXTRASYSTOLES WITH MORPHOLOGY OF COMPLETE RIGHT OR LEFT BUNDLE BRANCH BLOCK

These extrasystolic morphologies are obtained in any of the following conditions:

(*1*) *Ventricular Extrasystoles Produced Between the Beginning of the Ventricular Excitable Phase and the Ascending Limb of P (Between T and P)*: When a ventricular ectopic focus is discharged during the diastolic phase (between T and P), the activation of the whole heart depends on the ectopic stimulus (Fig. 11). The precocity of the premature stimulus (before the P wave) eliminates the possibility of an "addition of stimuli," a condition that occurs when the ectopic beat is originated between P and Q (see section on ventricular extrasystoles on page 359). The ectopic impulse "jumps" the "intraseptal barrier"[1] separating both septal masses and activating both ventricles. Ventricular asynchronism similar to that of complete bundle branch block is necessarily produced by the delay of the "jumping" of the wave as well as by the retardation of the activation of the non-stimulated ventricle.[1] We present the aforementioned reasons in order to explain the aberrancy and great duration of the ventricular ectopic beats. This morphology of third degree bundle branch block is found when the extrasystole arises in the free ventricular walls of both ventricles or in the septal mass.

In Figure 12 these types of premature beats

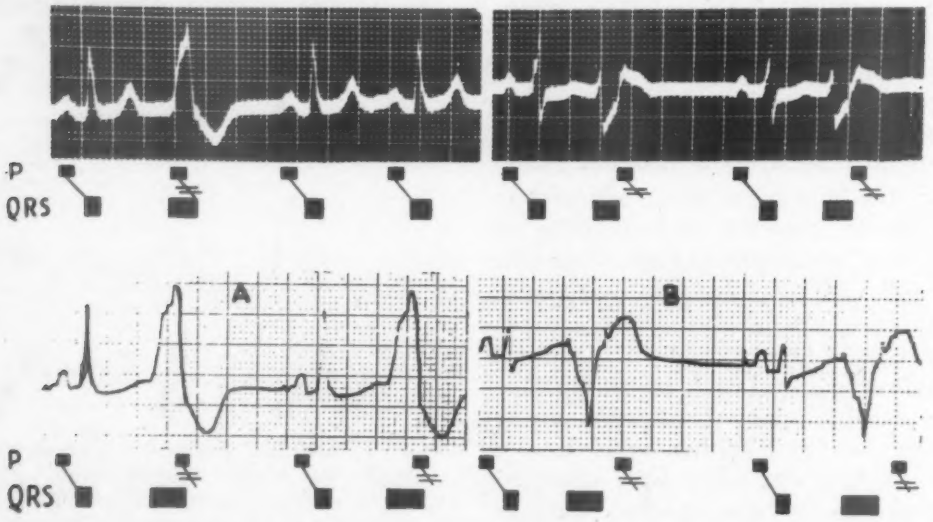

FIG. 12. Right (A) and left (B) ventricular premature beats. Upper row, clinical tracings; lower row, experimental reproduction (lead II).

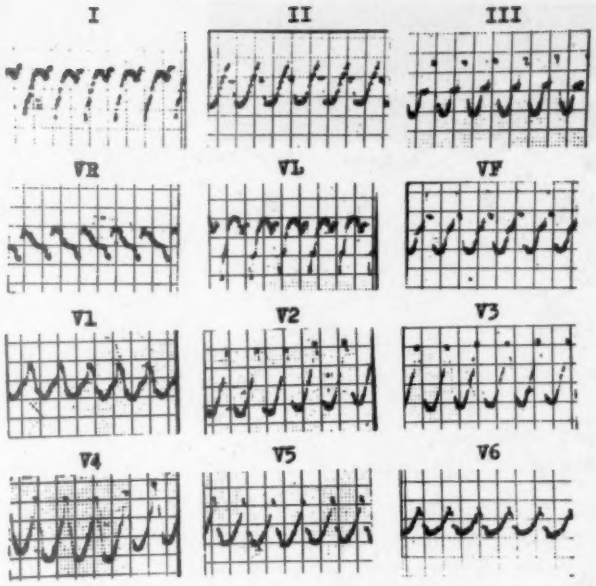

FIG. 13. Paroxysmal ventricular tachycardia originating in the superior and posterior portions of the interventricular septum.

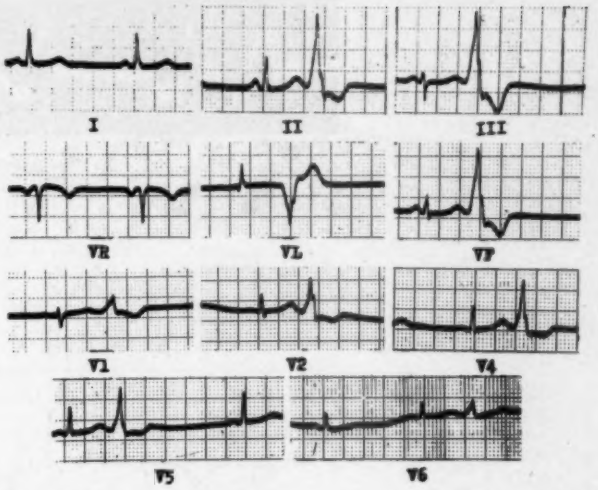

FIG. 14. Ventricular premature beats originating in the superior and posterior portions of the interventricular septum.

are shown. In (A) of the lower row, right ventricular beats produced experimentally in the dog's heart are recorded. In (B) of the same row, experimental left ventricular premature beats of another dog are presented. The upper row shows similar premature beats observed in clinical tracings.

Therefore, we have concluded that a ventricular premature beat registered between T and P shows a morphology of complete bundle branch block. Also, if a supposed ventricular premature beat has a morphology of incomplete bundle branch block (Figs. 1 and 2) and is registered between T and P, it is not ventricular.

We will, however, point out three possible but uncommon exceptions:

(a) *Premature beats arising in the "physiologic barrier" separating the right from the left septal mass.* Experimentally, the ectopic stimulus applied in this place reaches both ventricles almost simultaneously and the ventricular morphology of the premature beat tends to become normal.

(b) *A ventricular extrasystole originating in the upper and posterior portion of the interventricular septum.* The premature beat has a morphology that resembles second degree bundle branch block, but with a special characteristic of being positive in all precordial leads. It also has a sequence in activation similar to that of WPW syndrome type A.

Figure 13 shows paroxysmal ventricular tachycardia with positive QRS complexes in leads V_1 through V_6, suggesting that the ectopic focus is located in the posterior and superior portion of the interventricular septum. Postmortem study showed a non-specific myocarditis with predominance of the myocardial damage in the posterior and superior portion of the interventricular septum.

In Figure 14 ventricular premature beats with positive QRS complexes in all precordial leads

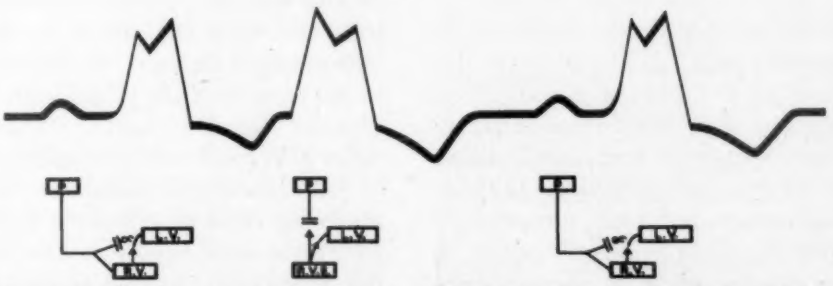

FIG. 15. Right ventricular extrasystole (R.V.E.) produced between T and P in the presence of left bundle branch block. The morphology of the ectopic beat is similar to that seen when there is sinus rhythm.

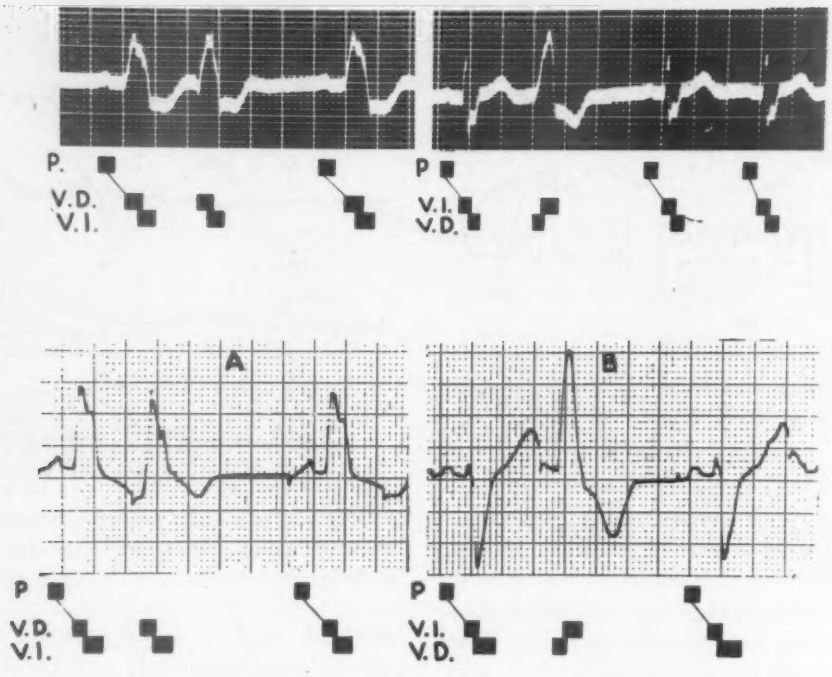

FIG. 16. Ventricular premature beats in the presence of right bundle branch block. The upper row shows clinical tracings. Tracings in the lower row were obtained experimentally in the dog's heart. A, left bundle branch block. B, right bundle branch block; the second beat is a left ventricular premature beat.

are shown. We believe that these ventricular premature beats originate in the high posterior portions of the interventricular septum, since experimentally such positivity is obtained only by stimulating those regions.

(c) *The third exception is contingent upon the degree of diastolic polarization that exists in the cells forming the "physiologic barrier."* Medrano and co-workers[3–6] found the "jump" of the wave from one ventricle to the other occurs in different durations from one dog to another (0.06 to 0.025 second). Rubio and Rosemblueth[7] demonstrated that it takes longer for an ectopic ventricular stimulus to cross the septal mass from right to left than from left to right; this explains why left ventricular extrasystoles are less bizarre than those emanating from the right ventricle.

(*2*) *Ventricular Extrasystoles Produced Between the Beginning of the Ventricular Excitable Phase and the Ascending Limb of P (Between T and P) in the Presence of Right or Left Bundle Branch Block:* These extrasystoles behave in the same manner as those described in the preceding section. There is no difference in their morphology when the ventricular ectopic beats appear in this part of the cardiac cycle in the presence (Fig. 15) or absence (Fig. 12) of bundle branch block.

Figure 16 shows ventricular premature beats in the presence of left and right bundle branch block. In the lower row the premature beats were obtained experimentally while the upper row is taken from clinical tracings. It is important to compare these morphologies with those seen when there is normal ventricular conduction (Fig. 12).

(*3*) *Ventricular Extrasystoles Produced Between the Ascending Limb of P and the Beginning of QRS, in the Presence of Incomplete Bundle Branch Block, when the Stimulus is Applied in the Ventricle Opposite to the Block:* The increase of the aberrancy of the complexes of sinus origin is due to the fact that the ectopic stimulus advances the activation of the ventricle opposite to the block, causing a greater asynchronism in depolarization of both ventricles (Fig. 17). It is obvious that the time the stimulus takes to cross the "physiologic barrier" is shorter than the delay in the descent of the stimulus in the incompletely blocked bundle branch; otherwise, morphologies of WPW syndrome will appear.

(*4*) *Ventricular Extrasystoles Produced Between the Ascending Limb of P and the Beginning of QRS, in the Presence of Complete Bundle Branch Block, when the Stimulus is Applied in the Ventricle Opposite to the Block:* If the block is complete the entire heart will be activated by the ectopic stimulus

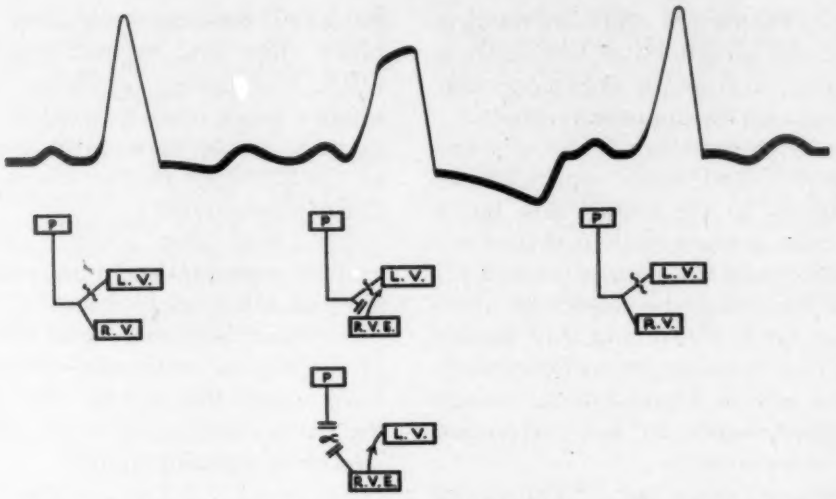

FIG. 17. Right ventricular extrasystole (R.V.E.) produced at the end of the P wave in the presence of incomplete left bundle branch block. Its morphology can be explained in two different ways: (1) the upper diagram represents a left ventricle activated in part by the normal supraventricular stimulus with summation of the effect of the ectopic beat that "jumps" the intraseptal barrier. (2) In the lower diagram the activation of both ventricles is produced by the ectopic stimulus due to complete A-V block that appears at the time of the discharge of the ectopic focus.

and the possibility of stimuli summation is eliminated.

(5) *Ventricular Extrasystoles Provoked in any Part of the Cardiac Cycle in the Presence of Complete A-V Block at the Time of the Discharge of the Ectopic Focus* (*Fig. 18*): The same conditions pertaining to the preceding section are valid in this type of premature beats. The complete A-V block eliminates the possibility of summation of stimuli since the normal supraventricular activation wave cannot reach the ventricles. Prinzmetal et al.[8] were unable to obtain WPW morphologies in the presence of complete A-V block for the same reason.

(6) *Supraventricular Extrasystoles in the Presence of Complete Bundle Branch Block:* In the presence of complete bundle branch block, a premature atrial ectopic beat has a ventricular complex exhibiting a morphology similar to that of the complexes of sinus origin; the premature stimulus encounters a delay in the blocked branch equal to that of the beats of sinus origin.

COMMENTS

The findings presented in this paper indicate that the universally accepted concept of the electrocardiographic diagnosis of ventricular extrasystoles has included many false ventricular premature beats which in reality are supraventricular in origin, and that many others considered as supraventricular are definitely ventricular. We will review a few definitions taken from several recent textbooks on electrocardiography.

Bellet[9] states that the duration of QRS in ventricular extrasystoles ranges from 0.08 to 0.19 second. This wide range is not compatible with our findings on ventricular activa-

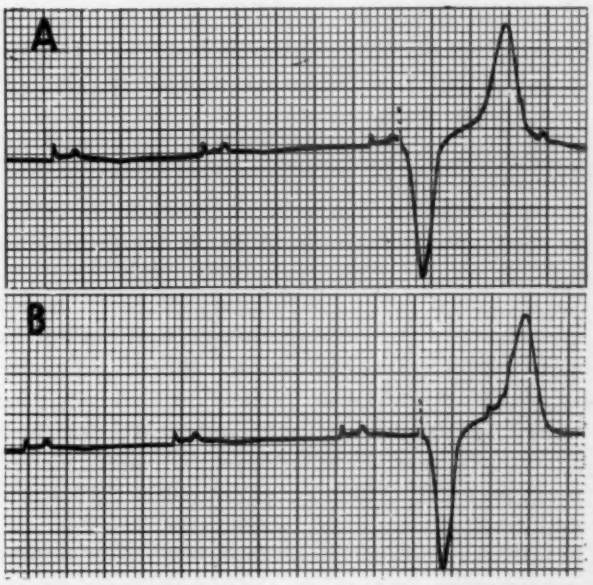

FIG. 18. Left ventricular extrasystoles provoked experimentally in the dog's heart after A-V block was obtained. In (A) the stimulus for the premature beat was applied during the P wave and in (B) it was applied after. Note the same morphology in both tracings.

tion: an ectopic ventricular stimulus requires 0.12 second or more to depolarize the ventricle where it originated, to cross the interventricular septum and to activate the opposite ventricle.

Katz[10] states: "A premature ventricular systole has a bizarre QRST with respect to the dominant complexes in the record and has a QRS which is more prolonged than that of the other beats (QRS equals 0.12 sec. or more. . .)." Nothing is said regarding the degree of aberrancy; although QRS duration of 0.12 second can be observed in extrasystoles with morphologies of first and second degree bundle branch block, these morphologies do not correspond to ventricular extrasystoles.

Scherf and Schott[11] point out: "The initial deflection, or QRS group, of a ventricular extrasystole is either higher or lower as well as wider than those of the sinus beats and commonly slurred and notched." This definition is also incomplete. The authors define neither the degree of ventricular aberrancy or its morphology; they speak of high or low voltage without correlating the degree of asynchronism in ventricular activation.

In consulting recent textbooks, we have found no mention of the cases in which the ventricular extrasystoles have a normal morphology and normal QRS duration under 0.10 second. It is admitted that some degree of asynchronism in ventricular activation exists in ventricular premature beats. We believe that the asynchronism is greater when there is no summation of stimuli and it diminishes when the supraventricular stimulus is added to the effects of the premature beat.

Because of the experimental work and the knowledge we have accumulated in ventricular morphologies, we are in a position to define a new concept of ventricular extrasystoles; we are unable to speak of the QRS duration, inasmuch as this is a function of the diastolic polarization of those cells that separate one septal mass from the other. We admit that no absolute definition can be proposed inasmuch as there are many variants in morphology depending on the time in the cardiac cycle when the premature beats are originated.

Our definition is as follows: Ventricular extrasystoles are those that show ventricular complexes with morphologies of advanced degree of block (third degree), when such extrasystoles are produced during the electrical diastolic phase between T and P. Those morphologies showing incomplete bundle branch block (first and second degrees) or normal QRS morphology are also ventricular premature beats when produced in the electrical diastolic phase between P and the beginning of QRS. Exceptions to this definition have already been stated.

The next step forward in electrocardiographic research should be to encourage finding a close relationship between the sequence of ventricular activation and the unipolar morphologies and vectorcardiographic curves. We have named this process "the understanding of the electrocardiogram" and its study "rationalized electrocardiography."

Summary

Experimental work is presented to prove that many extrasystoles, classically diagnosed as ventricular premature beats, are not. Most of them correspond to atrial or nodal extrasystoles with some degree of aberrancy.

On the other hand, there are ventricular premature beats with normal QRS duration and supraventricular beats with QRS duration greater than 0.12 second.

The differentiation of ventricular and supraventricular premature beats must be established by considering the morphology of the extrasystolic complex as well as the time in the cardiac cycle when the premature beat is recorded.

Definitions of ventricular extrasystoles from several recent textbooks are reviewed. A new definition is proposed based on experimental work performed in the dog's heart.

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Reviews

Heart Failure from the Point of View of Quantitative Anatomy*

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THE GOAL of cardiac pathology from the morphologic point of view should be to relate functional disorders of the heart to corresponding structural changes. Sixty years ago a famous dispute concerning the functional value of morphologic findings raged between the clinicians Krehl[1] and Romberg[2] and the pathologists Aschoff and Tawara[3] with exchanged roles, the clinicians championing a morphologic point of view and the pathologists defending a functional one. Krehl attributed failure of the hypertrophied heart to small foci of inflammation in the myocardium. Aschoff,[4] however, insisted that these small inflammatory infiltrates were unimportant from a functional point of view.

Aschoff was completely correct. The heart is a robust organ, and even the scars that develop in the myocardium after infarction need not materially impair its function. It has been shown in recent experiments[5-7] in dogs that 85 per cent of the right ventricular wall can be destroyed by electrocoagulation without producing an appreciable increase of right atrial or peripheral venous pressure. The right ventricle cauterized in this way even responds normally when the pulmonary artery is gradually constricted. From the opposite point of view, many patients with chronic cardiac insufficiency can show only very small qualitative changes in the myocardium on histologic examination. The question therefore arises as to whether or not there is any point in searching for morphologic substrates of cardiac insufficiency.

I believe this question can be answered in the affirmative and that the pathologic physiology of the heart can be understood only when the quantitative structural relations of this organ in health and disease are known. The quantitative approach to cardiac anatomy and physiology has much in common with cardiac roentgenology. Both disciplines are concerned with the measurable reversible and irreversible changes of size and shape of the healthy and diseased heart. Roentgenology has the advantage that it can make its measurements on the living heart. The pathologist's advantage lies in the fact that he can make measurements in the microscopic range. If it were possible to relate in detail the radiologic findings made *in vivo* with the quantitative findings at autopsy, this would be an important step forward in the functional evaluation of the human heart.

THE ANATOMIC BASIS OF VARIATIONS IN THE SIZE OF THE HEART

Comparison of Heart Size During Life and at Death: The first important question which is raised when roentgenologic and pathologic findings are compared is whether or not the heart has the same size at death as it had during life. It has been claimed that in the cat with an opened thorax, the size of the heart in systole is the same after death.[8] However, this does not appear to be true for the human heart. Friedman[9] has compared the size of the heart during life as measured roentgenologically with its postmortem size. He measured the total heart volume, the ventricular and atrial contents plus the volume of ventricular and atrial musculature. (Since by "total volume of the heart" is meant that surrounded by epicardium, the term "epicardial heart volume" will be used in the

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following discussion in order to avoid confusion.)

Figure 1 is drawn from Friedman's data.[9] The epicardial volumes of twenty-eight human subjects were measured. If the postmortem and *in vivo* heart volumes were the same, they would follow the lower line with a slope of 45 degrees. Instead, they follow the upper line with a slope of 56 degrees. It follows from this that the epicardial heart volume is about 50 per cent larger during life than it is after death, or conversely, about 33 per cent smaller postmortem than it is during life. The average difference in volume corresponds to the distance between the two straight lines in Figure 1. In a normal heart with a postmortem epicardial volume of 500 cc., the difference amounts to about 250 cc.; in the diseased heart with a postmortem volume of 1,000 cc., the difference is 500 cc., and in the heart with a postmortem volume of 2,000 cc., the difference is 1,000 cc.

The differences in volume of 250 to 1,000 cc. cannot be explained by systolic emptying of the two ventricles after death, even if we include a volume error of 20 per cent in the roentgenologic calculation of *in vivo* heart size by Kahlstorf's method.[10] The *in vivo* epicardial heart volume in man must lie between the two straight lines of Figure 1. This must mean that the living heart is larger in systole than it is after death, and that the amount of residual blood in the heart is smaller postmortem than it is in systole during life.

Relation Between the Dimensions of Myocardial Fiber and the Weight and Width of the Ventricles: In forty human hearts of various age groups, both normal and abnormal, the average distance between the Z-bands of the myocardial fibers was measured after death. (The distance between Z-bands is also the length of the sarcomere.) It was found that in all cases this distance was 1.4 μ in left ventricular fibers and 1.5 μ in right ventricular fibers. There was no significant difference in normal, hypertrophied or pathologically dilated hearts[11] (Table I). Furthermore the Z to Z distance proved to be the same in a wide variety of animals (cattle, goat, dog, guinea pig, rat and chick).[12–14]

Hort[13,14] has studied this relationship in greater detail in the thin-walled right ventricle of fresh hearts of the guinea pig and the dog with the following results: (1) with increased filling of the ventricle the geometrical shape of its surface does not change, and (2) during increased filling the average distance between

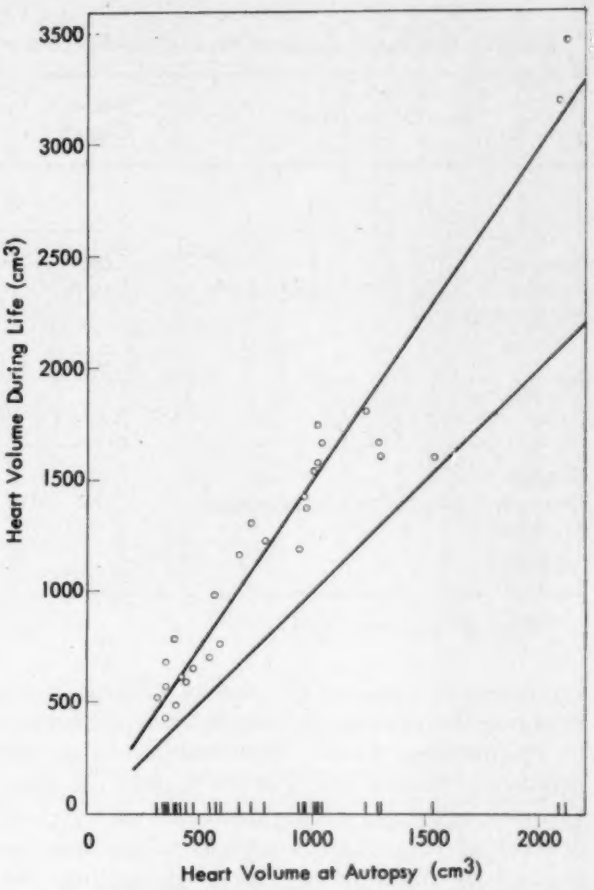


FIG. 1. Comparison of *in vivo* and postmortem heart volumes in twenty-eight subjects plotted from data of Friedman.[9] *Ordinate, in vivo* volumes measured by x-ray. *Abscissa*, postmortem volumes. (From: LINZBACH, A. J. Fifth Freiburger Symposium, p. 94. Berlin, 1958. Springer Verlag.)

adjacent Z-bands is proportional to the square root of the ventricular surface area. However, this apparently simple behavior of the muscle fibers is the result of a complex structural alteration. Let us imagine a very thin muscular shell within the right ventricle consisting of only a single layer of muscle fibers. In such a shell all muscle fibers must be parallel. With dilatation, the surface area of this shell will become uniformly larger. Since the muscle fibers run parallel, they can lengthen in only one direction and must become thinner in so doing. But the surface area of the shell is increased not only longitudinally but also laterally, that is, perpendicular to the course of the fibers. Therefore, as the muscle fibers are stretched longitudinally, the interstitial spaces should become wider to a corresponding degree. These spaces do not remain empty. If the muscle shell should have more than one layer of parallel fibers, the muscle fibers of the adjacent muscle

TABLE I

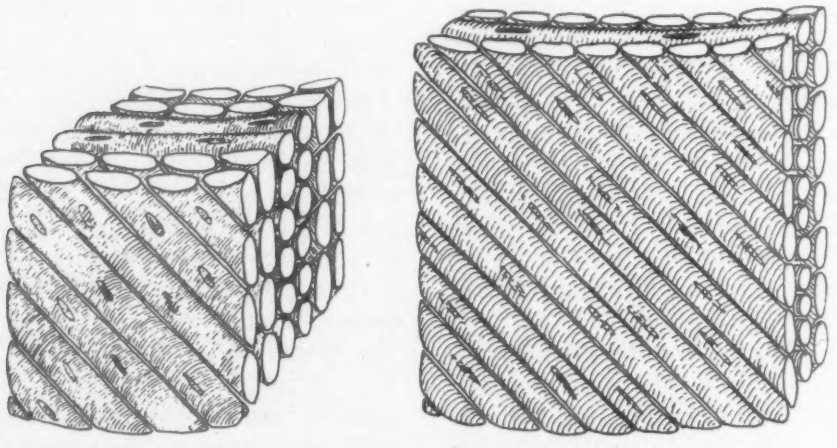
Distance between Z-Bands of Myocardial Fibers in Normal, Hypertrophied and Pathologically Dilated Hearts

Condition of Heart	No. of Cases*	y = Mean Z to Z Distance	σy	$\frac{\sigma M = \sigma y}{\sqrt{N}}$
		Left Ventricle		
Normal	19	1.36 μ	0.094	0.022
Concentric and eccentric hypertrophy	16	1.45 μ	0.096	0.024
Myocarditis	5	1.40 μ	0.032	0.014
Mean	...	1.40 μ	0.100	0.016
		Right Ventricle		
Normal	19	1.45 μ	0.110	0.027
Concentric and eccentric hypertrophy	16	1.53 μ	0.110	0.028
Myocarditis	5	1.55 μ	0.020	0.014
Mean	...	1.49 μ	0.113	0.01

* Total of forty cases.

layer would slip into the spaces (Fig. 2). By counting the number of fibers from endocardium to epicardium, Hort[14] demonstrated that the number of muscle layers in the wall of the right ventricle of the guinea pig decreases with greater degrees of dilatation, which can only be explained by fibers of one layer sliding into the spaces between fibers of an adjacent layer. Weitz[15] had previously observed such a decrease of the number of layers of muscle fiber with increasing dilatation of the ventricle but was unable to offer an explanation for it. Incidentally, this rearrangement of fibers with different right ventricular volume[15] does not influence the validity of the structural implications of Starling's law because the increased lengths of the muscle fibers remain proportional to the square root of the ventricular surface area. These reversible structural changes and rearrangements of fibers during systole and diastole are important and must be taken into consideration in explaining the mechanism of active diastole.

Present studies indicate that these processes are even more complicated in the thick-walled left ventricle. Using an improved interferometric measuring method, Hort[13,14] also succeeded in confirming for the left ventricle the assumption[16,17] that during filling and emptying the inner fibers change more in length than do



A B

FIG. 2. Changes in right ventricular fibers of the guinea pig on acute dilatation. A, systole of the normal heart. B, the same region when acutely greatly dilated. (From: HORT, W. *Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch.*, 23: 343, 1957.[14])

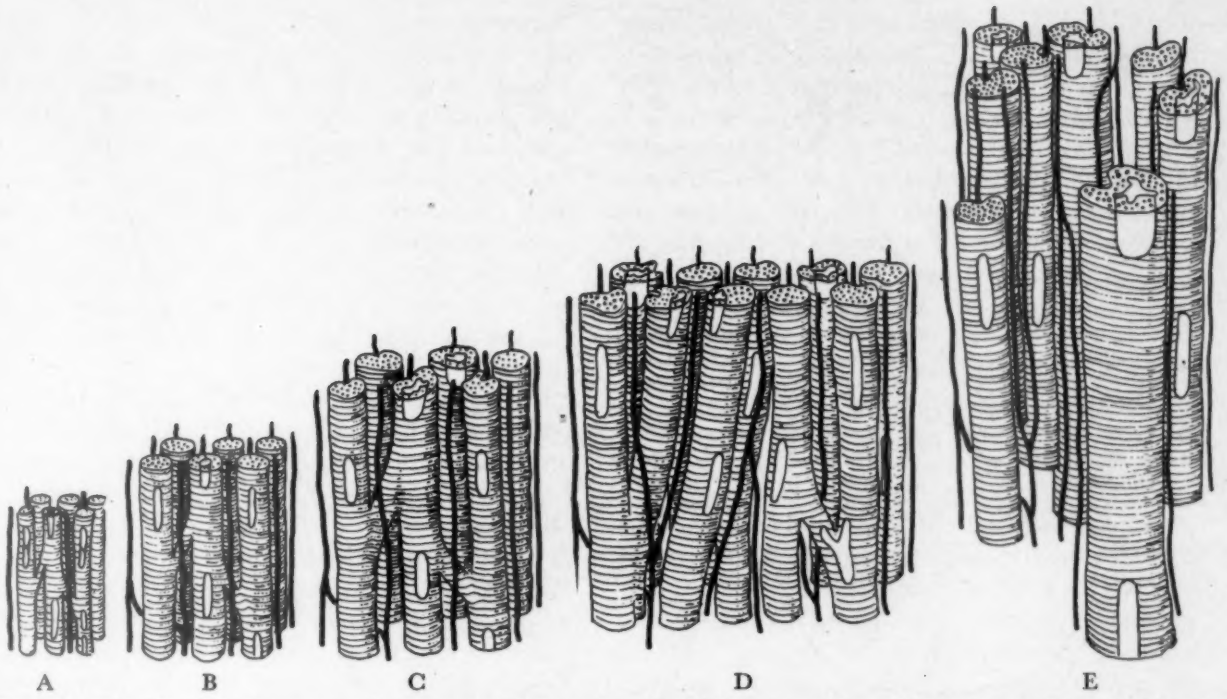


FIG. 3. Growth of six heart muscle fibers and their capillaries in the myocardium of the left ventricle. Weights in parentheses. A, infant (heart, 15 gm.; left ventricle, 7 gm.). B, adult (heart, 300 gm.; left ventricle, 100 gm.). C, athlete (heart, 500 gm.; left ventricle, 200 gm.). D, concentric pressure hypertrophy: the same group of muscle fibers after longitudinal cleavage (heart, 650 gm.; left ventricle, 400 gm.). E, decompensation. Eccentric hypertrophy. Structural dilatation. Some muscle fibers have disappeared. The surviving muscle fibers show compensatory hypertrophy with rearrangement. Between the muscle fibers is scar tissue (heart, 900 gm.; left ventricle, 500 gm.). (From: LINZBACH, A. J. Fifth Freiburger Symposium, p. 94. Berlin, 1958. Springer Verlag.)

the outer. The experiments indicate that length of the sarcomere is a function of the stretching and contraction of the fibers.[11] We estimate that normal ventricular filling involves a change from a sarcomere length of 1.5 μ to one of about 2 μ. The maximum lengthening still compatible with normal function is probably little beyond 2 μ, and adaptations of heart function by increasing the stretching of muscle fibers appears to be very limited (Fig. 5B).

ROLE OF GROWTH PROCESSES IN DETERMINING THE SIZE OF THE HEART

Before we pass from a discussion of the anatomy of acute changes in heart size to a discussion of chronic, partially irreversible changes it is necessary to consider briefly the quantitative relations of normal heart growth. In earlier studies from our laboratory it was shown that all normal human hearts have essentially the same number of muscle fibers and nuclei, and that, although the right ventricle is only half as heavy as the left ventricle, it has roughly the same number of fibers and nuclei. The right ventricular fibers are not only thinner than those of the left ventricle, but are also arranged differently, with fewer fiber layers (Fig. 4A).

Comparison of Muscle Fibers and Capillaries in Infant and Adult Hearts: The schemata in Figure 3 are drawn to scale from data previously published.[18–26] They show a group of muscle fibers and capillaries of the human ventricle at different stages of growth. Figures 3A and 3B show the fibers of an infant and an adult heart. During normal postnatal growth of the heart the component elements of the myocardial syncytium become wider and longer but maintain a fixed length-width ratio. No multiplica tion of fibers takes place with body growth. Since the Z-band to Z-band distance is the same at all ages, the increased length must be accompanied by an increase in the number of the sarcomeres.

In the heart of the infant there is a capillary for every four or five myocardial fibers.[27–29] This means there are four to five fibers enclosed in each space of the capillary network (Fig. 3A). In the heart of the adult, on the other hand, there is a capillary adjacent to each muscle fiber, and there is only one fiber in each space of the capillary network (Fig. 3B). Since the number of fibers is the same in the adult as in the infant, there must be a fourfold increase in

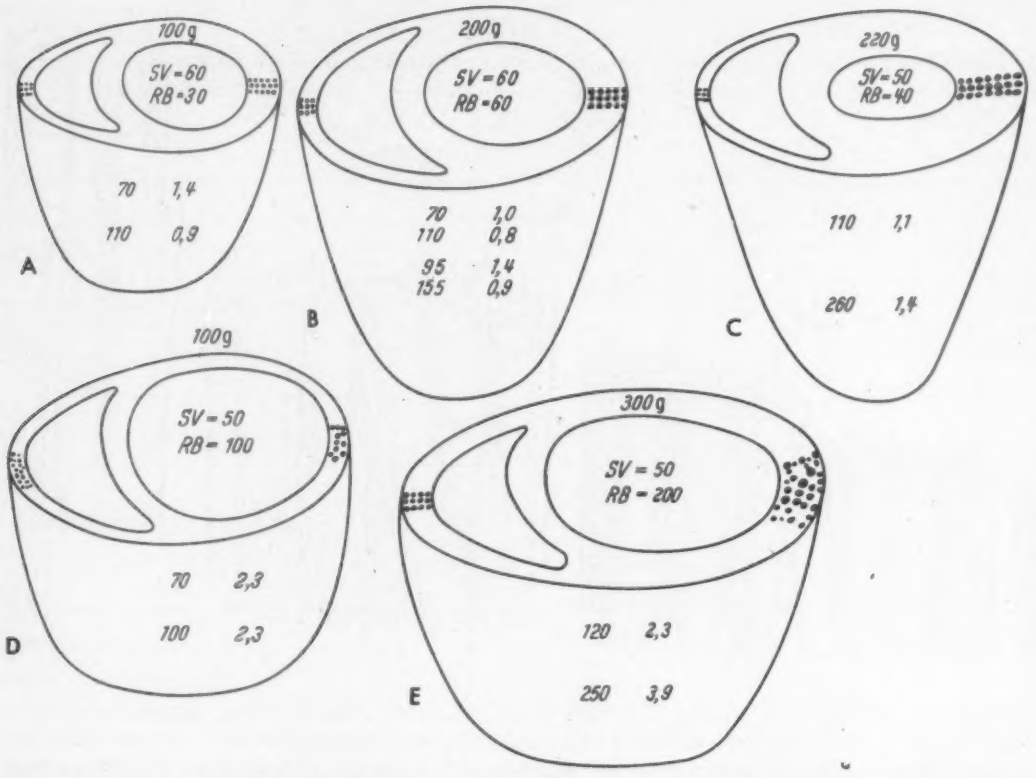


FIG. 4. Relationship between heart muscle mass (figures in parentheses), chamber volume and tension. A, normal subject (300 gm.). B, athlete (500 gm.). C, concentric hypertrophy due to hypertension (550 gm.). D, plastic structural dilatation (300 gm.). E, eccentric hypertrophy (650 gm.). Black dots on figure illustrate relative distribution and numbers of fibers on cross section. SV = stroke volume. RB = residual volume. Numbers on surface of cross section = weight of ventricle. Numbers on ventricular surface = *left*, diastolic and systolic pressures; *right*, force of tension in 10^5 dynes $cm.^{-2}$. (From: LINZBACH, A. J. Bad Oeynhauser Gespräche III. Berlin, 1958. Springer Verlag.)

the number of capillaries in the left ventricle of the adult. It is interesting that in spite of this growth of the capillary network, the width of the spaces of the network is essentially the same in the heart of the adult as in that of the infant. In other words, the cross-sectional area of one adult muscle fiber is occupied by four fibers in the infant (compare Figs. 3A and 3B).

Myocardial Fibers in Physiologic Hypertrophy: When the work of the heart is chronically increased, as in athletes or laborers who do heavy physical work, the weight of the heart increases from a normal weight of 300 gm. to as much as 500 gm. The left ventricular weight increases from a normal of about 100 gm. to 200 gm. Such an increase in heart weight to 500 gm. has been named *physiological hypertrophy*.[18] The increase in weight is not due to an increase in number of fibers; the fibers simply become thicker and longer, as an extension of the physiologic growth described earlier. The spaces in the capillary network become only slightly wider. It is as if the normal myocardium were viewed through a magnifying lens (Figs. 3B, 3C and 4B), if we disregard the increase in number of sarcomeres and the fact that the nuclei remain practically the same length, while the area of their cross sections increases.

Myocardial Fibers in Pathologic Hypertrophy: On the other hand, when the work of the heart is increased to a greater extent by some pathologic mechanism such as hypertension or aortic valvular disease with, unlike in the athlete, the increased work continuing day and night, the weight of the heart will exceed 500 gm. If the increased work is due to valvular insufficiency, a *volume hypertrophy* results with a larger than normal ventricular chamber and residual blood volume (eccentric hypertrophy). On the other hand, when the increased work is due to resistance to ejection as in aortic stenosis or hypertension, a *pressure hypertrophy* (Fig. 4C) results with the ventricular chamber size and residual blood volume remaining normal (concentric hypertrophy). Under either circum-

stance the total weight of the heart may reach 1,000 gm. or more with a left ventricular weight of 400 gm. or more. This has been named *pathologic hypertrophy*. As will be pointed out shortly, the method of growth of the myocardium in this type of hypertrophy is different from that in physiologic hypertrophy. The margin between the two types of hypertrophy is a narrow one. We have considered 500 gm. the *critical heart weight*, and a left ventricular weight of 200 gm. the *critical ventricular weight*.

Figures 3D and 4C show the changes in the left ventricular myocardium in concentric pressure hypertrophy. There is an absolute increase in the number of fibers, nuclei and capillaries with little further thickening of the muscle fibers. The increase in the number of muscle fibers appears to be due to longitudinal cleavage between points of anastomosis of the myocardial syncytium (Fig. 3D). As a result, the number of fiber layers may be greatly increased in marked concentric hypertrophy. But the epicardial volume may not be significantly increased because the increased fibers encroach on the endocardial volume resulting in a small, narrow ventricular cavity and the residual blood volume remains normal. The number of capillaries increases to the same extent as the number of muscle fibers, and therefore the ratio of one capillary per fiber remains the same; the width of the spaces in the capillary network is not essentially different from that seen in physiologic hypertrophy.

Coronary Supply in Pathologic Hypertrophy

Our findings contradict a theory that prevailed for many years regarding the mechanism of myocardial hypertrophy. It was long thought that there is no increase in the number of myocardial fibers in pathologic hypertrophy, but that the fibers simply become progressively thicker. In this theory, originally propounded by Eppinger,[30] it was further believed that the capillaries remain fixed in number, and, with the muscle fibers becoming thicker and thicker, the distance from the capillary to the center of the fiber would become too great for efficient diffusion of oxygen. This was thought to account for the heart failure that so often accompanies marked hypertrophy.[28,31] Büchner[32,33] and his students have found additional indirect evidence that the failure of hypertrophied hearts is related to myocardial hypoxia. But, it is now well established that in pathologic hypertrophy the capillary-to-fiber ratio is not abnormal and the diffusion distance is not essentially greater than it is in physiologic hypertrophy. Therefore, without taking into consideration the factor of capillary length, the explanation for the myocardial hypoxia of hypertrophy is not to be found in the width of the spaces of the capillary network but must be related to some aspect of the coronary arteries and their branches.

Schoenmackers[34] studied the relationship between total heart weight and the diameters of the coronary arteries and found that the two were linearly related only up to a heart weight of 500 gm. Vogelberg[35] has recently confirmed this for the diameters of the coronary ostia. Bäurle[36] showed that the epicardial branches of the coronary arteries are preferential sites of atherosclerosis in patients with hypertension. Kathke[37] as well as ourselves[18] noted frequent changes in the smaller intramural branches as well. However, normotensive patients in the seventh decade with normal fiber diameters also commonly show atherosclerotic changes in the intramural branches of the coronary arteries.[38–40] It is our belief that the fact that the coronary arteries and coronary ostia are too narrow for the size of the heart in pathologic hypertrophy is the main cause of hypoxia in these hearts.

In summary, the insufficient widening of the coronary ostia and the inadequate growth of the coronary arteries and their branches combined with a predilection for arteriosclerotic changes in these vessels restrict coronary perfusion as hypertrophy becomes greater. As this discrepancy increases the coronary reserve is finally exhausted, leading to disturbances of myocardial nutrition. This in turn leads to the focal necroses described by Büchner[32] in hypertrophied hearts, and over the course of years scars form and the result is the picture of focal and diffuse fibrosis. As these myocardial changes develop the chamber dilates and the residual blood volume increases. Concentric hypertrophy gives way to eccentric hypertrophy and the clinical picture of chronic decompensation appears.

The Anatomic Bases of Dilatation

The change from concentric to eccentric hypertrophy has generally been ascribed to what is called "myogenic" dilatation, where the damaged fibers become more and more stretched

in diastole. We have studied this in a number of hearts with eccentric hypertrophy and greater than normal residual blood volumes and have found that the muscle fibers are by no means overstretched. The Z-band to Z-band distance averaged 1.4 μ, which is the same as in the normal and the undilated hypertrophied heart (Table I, Figs. 3B to 3E). Furthermore, it was found that the average distance between nuclei in the middle of a fiber was the same for eccentric as for concentric hypertrophied hearts of the same weight. The dilatation of these hearts must then involve plastic structural changes within the myocardium and particular rearrangements of the muscle fibers with respect to each other. These rearrangements take place in part radially across the wall and in part tangentially with the wall, for there is a smaller number of fiber layers across the wall in eccentric hypertrophy than in concentric hypertrophy when the total heart weight is the same (Fig. 3E).

It is possible that the dilatation is hastened by the focal hypoxic necroses that are commonly seen in the myocardium in eccentric hypertrophy. The way this might take place is that, with an increased systolic tension in the surviving fibers, those regions where the fibers are soft and plastic from hypoxia become overstretched during isometric contraction. This forms a vicious circle with the ventricle undergoing more and more such regional, irreversible "overstretch" over the years. We have called this *irreversible plastic dilatation.* The residual blood volume is increased, but, in contrast with the normal heart and the athlete's heart, the increased residual blood volume cannot be mobilized. We have, therefore, referred to the *mobilizable residual volume* of the athlete's heart and the *fixed residual volume* of plastic dilatation. In the scarred heart with eccentric hypertrophy the myocardial fibers may be wider in diameter than in concentric hypertrophy of the same degree because of compensatory hypertrophy of the surviving fibers (Figs. 3E and 4).

Of course, this type of dilatation occurs not only when concentric hypertrophy evolves into eccentric hypertrophy; it is also seen in the volume hypertrophy of aortic insufficiency and especially when associated with endocarditis and myocarditis. Further, our studies suggest that the dilatation without hypertrophy seen in diphtheritic myocarditis and chronic coronary arteriosclerosis is also of this type (Table I, Fig. 4).

Relation Between the Work of the Heart and Its Anatomy

If we know the quantitative morphologic changes that take place in different cardiac disorders it should be possible to calculate, in a very general way, the force developed in systole per unit cross sectional area of the myocardium for these disorders, using the approaches of Weitz[41,42] and Burch et al.[43] Of course, such calculations can only be approximations and give only relative information for the various cardiac conditions.

The total force of tension of the left ventricle is most easily calculated by considering the ventricle to be a sphere with uniform thickness of the wall. With this simplification the total force of tension in dynes becomes the product of the intracavity pressure in dynes $cm.^{-2}$ times the area of the circular plane representing the width of the ventricular wall at its equator as shown in Figure 4. The area of the circular plane is one-fourth the internal surface area of this idealized left ventricle. For clarification, the force of the left ventricle is roughly equal to the intracavity pressure times one-fourth its internal surface area. The tension force per square centimeter of cross-sectioned heart muscle is obtained by dividing the total force of tension in dynes by the area of the circular ring formed by the ventricular wall, and is expressed in dynes $cm.^{-2}$

The Normal Heart: The normal left ventricle may have a weight of 100 gm. and a volume at end-diastole of 90 cc. with a 60 cc. stroke volume and a 30 cc. residual volume. During isometric contraction the ventricular pressure reaches the diastolic level of the aortic pressure, for example, 70 mm. Hg. For a ventricle of these dimensions to reach this internal pressure a force of 1.4×10^5 dynes $cm.^{-2}$ is required (Fig. 4A). Then, to eject the stroke volume the internal pressure must rise to 110 mm. Hg. The internal surface area of the ventricle decreases faster than the pressure rises. The force is therefore smaller toward the end of systolic ejection than it is during isometric contraction. In the example under consideration the end systolic force decreases to 0.9×10^5 dynes $cm.^{-2}$

Physiologic Hypertrophy: When the normal left ventricle undergoes physiologic hypertrophy (as in the athlete's heart) the ventricular weight may be 200 gm. with an end-diastolic volume of 180 cc. The resting stroke volume would still be 60 cc., according to the studies of Reindell

and co-workers.[44-46] The increased residual volume of the left ventricle is secondary to the physiologic hypertrophy and there is no need to invoke "regulative dilatation" for its explanation. The increased residual volume can be mobilized on exertion.

Kirch[47] has shown that when the left ventricle enlarges there is first elongation of the inflow and outflow tracts. The residual volume in physiologic hypertrophy would therefore more likely be only twice the range of the normal residual volume, giving an end-diastolic volume of 120 cc. instead of 180 cc. With the same arterial pressures as in the earlier example the force per square centimeter of cross section of ventricular wall would be 1.0×10^5 dynes cm.$^{-2}$ at the end of the isometric contraction and 0.8×10^5 dynes cm.$^{-2}$ at the end of ejection. For example, during exertion with the arterial pressure rising to 155/95 mm. Hg and the stroke volume to 80 cc., the force at the end of the isometric contraction would be 1.4×10^5 dynes cm.$^{-2}$ and 0.9×10^5 dynes cm.$^{-2}$ at the end of ejection. We can see, then, that the athlete's heart at rest develops less force per unit of muscle than does the normal left ventricle to do the same work. Only on exertion is force per unit of muscle the same as for the normal heart (Fig. 4B).

Concentric Hypertrophy: In concentric hypertrophy the cross sectional area of muscle is greatly increased with no change in the size of the internal cavity. We will see that from an energy point of view this is ideally suited for ejecting a normal stroke volume against a high resistance as in compensated aortic stenosis or hypertension. In the example of Figure 4C we will assume a left ventricular weight of 220 gm. and an arterial pressure of 260/110 mm. Hg. The end-diastolic volume would be normal, 90 cc., with a 50 cc. stroke volume and a 40 cc. residual volume. At the end of isometric contraction a force of 1.1×10^5 dynes cm.$^{-2}$ would be generated per square centimeter of cross section of ventricular muscle, and at the end of systole 1.4×10^5 dynes cm.$^{-2}$ This last value is the same as for the normal ventricle at the end of isometric contraction. From these calculations we see that while for the normal heart the maximal force occurs at the end of isometric contraction, for the pathologically hypertrophied hearts the maximal force is generated at the end of systolic ejection. Burch et al.[48] also pointed out this reversal.

Eccentric Hypertrophy: In this condition the ventricular muscle mass is increased, but the residual volume is greater and the ventricular wall is therefore relatively thin. In our example (Fig. 4E), we assume a left ventricular weight of 300 gm. with an end-diastolic volume of 250 cc., a stroke volume of 50 cc. and an arterial blood pressure of 250/120 mm. Hg. Under these circumstances the force generated must reach 2.3×10^5 dynes cm.$^{-2}$ at the end of isometric contraction and 3.9×10^5 dynes cm.$^{-2}$ at the end of ejection; during ejection still higher values must be reached. This force is three times that required of the normal left ventricle to eject the same amount of blood. The greater force necessary is due both to the higher than normal resistance to ejection and the reduced muscle cross section for that amount of residual volume. In other words, when the residual volume increases, the inner surface area of the ventricle is increased more than is the muscle cross section area, and that accounts for the greater unit force required on systole.

Of course, in such a heart the cross section area is not entirely composed of muscle for there are areas of necrosis and scarring. This would cause the force required per unit of effectively contracting muscle to be still greater. It will be noted in Figure 4E that in this heart the right ventricle also shows hypertrophy and dilatation, due to the elevated pulmonary artery pressure secondary to the left ventricular failure.

Myocarditis: In acute and subacute myocarditis there is dilatation without hypertrophy and as a result the force required for isometric contraction and ejection is greater than for the normal heart. If we assume a left ventricular weight of 100 gm., a blood pressure of 100/70 mm. Hg, an end-diastolic volume of 150 cc. and a stroke volume of 50 cc., we obtain a force for end-isometric contraction of 2.3×10^5 dynes cm.$^{-2}$ and for end-ejection of 2.3×10^5 dynes cm.$^{-2}$ (Fig. 4D). Here, too, perhaps not all of the cross section area consists of effectively contracting muscle and the force required may still be greater than the calculation. Dilatation due to coronary artery disease would have a more or less similar force requirement.

Tension of the Heart Muscle Fibers as a Factor Controlling Heart Growth

With Bohnenkamp[48] we believe that the most important factor controlling the size of the heart muscle mass is not the work done by the heart but the systolic force of tension of the heart muscle fibers. From studies of heart-lung

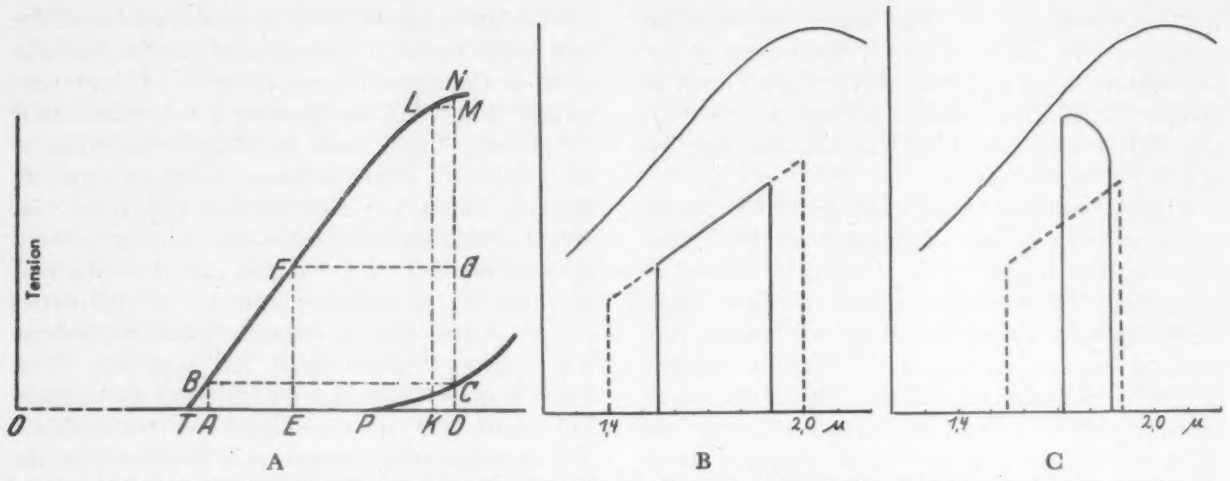


FIG. 5. A, length-tension diagram after Fenn.[50] B, schema of a work diagram of a muscle fiber of a normal left ventricle. Ordinate, tension; length on abscissa, sarcomere; upper line, maxima of tension (after Fenn); lower dotted lines, range of functional adaptation. C, similar work diagram of a muscle fiber from a left ventricle with structural dilatation. (From: LINZBACH, A. J. *Morphologische Gesichtspunkte zur Herzdynamik.* Bad Oeynhauser Gespraeche III. Berlin, 1959. Springer Verlag.[51])

preparations it has been shown that when a ventricle is overloaded a "tonogenic" overstretching of the muscle fibers takes place and the force generated per unit cross section of the muscle must increase; the heart works on the upper limb of Starling's curve and efficiency is improved (Fig. 5B). If the overload is continued, as it is in cases of hypertension, the "overstretching" is replaced by fiber hypertrophy. This hypertrophy increases until the force generated per unit cross section returns to normal values for the same increased amount of work. This normal value of force of tension per unit of cross section of myocardium must represent some subtle energy-economy maximum. During the acute dilatation of temporary overloading the muscle mechanism must not be optimal even though there is an improved efficiency because otherwise it would be hard to understand why more long term overloading should lead to hypertrophy.

These considerations indicate that the concept of so-called "tonogenic dilatation" must be revised. The fact that there is a close correlation between the work and the size of the heart indicates that "tonogenic dilatation," the adaptation that takes place with dilatation in accordance with Starling's law, must take place over only a very small range of variation in cardiac output and be very temporary in man. It seems likely that the average diastolic length of the normal myocardial fiber lies near the value Gremels[49] identified on the Starling curve. The cardiac output can increase when the fiber length is greater than this, but the curve of increasing efficiency has already flattened at this point.

If it is the tension that the heart muscle fiber performs that determines its size, the athlete would have to stay in constant training to maintain his physiologic hypertrophy. With a long period of rest, the force per unit of muscle would be less than that of even the normal heart at rest and the heart would diminish in size. Hort[24] demonstrated that this was so in rats trained to run. Perhaps the gradual rise in arterial blood pressure with age prevents the athlete's heart from returning to normal size when he discontinues his program of exercise.

The tension of the heart muscle fibers also determines the weight of the heart in pathologic hypertrophy. The hypertrophy occasionally seen in patients with chronic coronary artery disease and with myocarditis must also be mentioned. Here, presumably, the dilatation alone brings about an increase in required tension per unit of surviving muscle, partly offset by compensatory hypertrophy.

CAUSES OF HEART FAILURE IN THE PRESENCE OF PLASTIC STRUCTURAL DILATATION

It has been shown that the force of contraction of the heart is affected most when the residual volume is increased. This is confirmed by clinical experience, for cardiac disorders with pathologic dilatation which have increased fixed residual volume are usually accompanied by acute or chronic cardiac insufficiency. It is true of eccentric volume hypertrophy, eccentric pressure hypertrophy, and for

hearts with myocarditis and coronary sclerosis. The difference between these hearts and those without decompensation (the normal heart, athlete's heart, compensated volume hypertrophy and concentric pressure hypertrophy) lies in the anatomic characteristics of dilatation. These characteristics are of three types: functional adaptation, structural adaptation and muscle mechanics.

(*A*) *Functional Adaptation:* Experiments with heart-lung preparations have shown that in acute overloading of the healthy heart there is a reversible overstretching of the myocardial fibers with improved efficiency. The question arises whether this mechanism of functional adaptation may be useful equally for hearts with pathologic dilatation. We believe that this is not the case for several reasons. First, the functional adaptation is present only during short temporary overloading. Patients who have heart disease with structural dilatation are subjected to permanent overloading and therefore only compensating mechanisms of long duration could be effective. Second, the residual volume is already increased in the dilated heart; additional dilatation by overstretching of muscle fibers would but further increase the contracting force necessary for a given stroke volume and so facilitate additional structural dilatation. Third, the overstretching of heart muscle fibers involves increased consumption of oxygen by the myocardium. Since we know that in most cases of chronic heart disease with structural dilatation there is already a relative deficiency of oxygen, a further increase in consumption of oxygen might not be beneficial. Therefore, it is reasonable to conclude that in these cases additional dilatation may be unfavorable for heart function, and the presence of structural dilatation in these hearts progressively inhibits the possibility of functional adaptation.

(*B*) *Structural Adaptations:* It has been shown that the compensated heart can meet the challenge of chronic overloading only when a compensatory hypertrophy or hyperplasia of the myocardium develops. In this state of compensation the heart as a whole works on a higher level but with the same mechanical conditions for the muscle fibers as in the normal heart. However, this is not possible in the heart with advanced structural dilatation. In such a heart not only functional but also further structural adaptations which might take place to meet the challenge are already exhausted. The reason for this is that in structural dilatation the effective muscle mass of the heart is already inadequate to support a work level with the same muscle mechanics as in the normal heart (Fig. 4D). The effective muscle mass is often further reduced by the loss of myocardial fibers, either as a result of inflammation or hypoxia, depending upon the underlying disease. Under the conditions of inflammation or hypoxia the need for greater contractile force from the uninvolved muscle areas increases more rapidly than compensatory hypertrophy or hyperplasia can take place. As a result, a vicious circle is started and the relative area of the muscular cross section of the ventricular wall becomes smaller as the chamber size becomes relatively larger. One could say that the difference between the force of tension calculated for a heart having these anatomic dimensions and the amount of force actually produced indicates the degree of decompensation.

(*C*) *Muscle Mechanics:* Work is the product of force times distance. Applying this to the heart, work becomes proportional to the contractile force of the ventricle in dynes times the linear shortening of the muscle fibers during systole. For a given stroke volume the muscle fiber shortens relatively less as diastolic volume becomes larger. Therefore, for the same pressure and stroke volume (i.e., the same work), contraction of the fibers will involve a relatively small force but considerable shortening in the narrow, small heart and a large force but relatively little shortening in the dilated heart. It follows that in the compensated heart, work is done with relatively small force but great shortening, while in the structurally dilated heart with increased fixed residual volume, work is done with relatively little shortening but with great force. But, since the length of the sarcomeres is the same in normal and structurally dilated hearts, the mechanical working conditions of the muscle fibers in dilated hearts are comparable to those of skeletal muscle when the load becomes greater and the shortening less (Fig. 5A).

It might be objected that as far as the individual fibers are concerned it matters little whether the work is done with large or small force, great or slight shortening. However, the findings in the compensated heart indicate that the myocardium does maintain a definite relation between the force developed and the amount of shortening. From the standpoint of

the energy of the fiber there is evidently an optimal relationship between the two.

This optimal relation between force and shortening is well illustrated in Fenn's studies[50] of muscle mechanics, diagramed in Figure 5A. With a constant initial fiber length (D), a small load is first compensated for by a slight isometric tension (DC), followed by a great shortening (CB). With increasing loads the isometric tensions rise (DG and DM) while the shortenings decrease (GF and ML). The work per unit muscle corresponds to the area given by the product of isometric tension times the amount of shortening. In this example the maximum of work is obtained when the load is of medium size, for the areas DCBA and DMLK are smaller than the area DGFE. But the theoretical maximum of work would be performed by the muscle when first, a great isometric tension was created with a heavy load (DN) and then, in the course of shortening, the load became continually smaller (NT). In this case the work would approximate the area DNTD. These optimal mechanical conditions are approximately those of the muscle fibers of the normal left ventricle (Fig. 5B). We may conclude that the unit muscle weight of a normal left ventricle with normal dimensions performs a maximum of work.

But, in a left ventricle with structural dilatation, the work done by the unit muscle weight is smaller than that of a normal left ventricle (Fig. 5C). For a given amount of work the muscle mass must be greater in a dilated left ventricle than in a normal one. At each stage in progressive structural dilatation the muscle fibers are called upon to contract with greater force without increased stretching. In addition to this the effective muscle mass diminishes due to inflammation or hypoxia; synchronously the work performed per unit muscle weight decreases. Therefore, the stroke volume falls until finally a threshold value is reached at which the myocardium can no longer convert the energy released by oxidation into adequate work and insufficiency develops.[51]

This view is in opposition to the prevailing theory of cardiac insufficiency based upon Starling's law. In this theory the results obtained by comparing fiber length and consumption of oxygen in acute experiments with heart-lung preparations are simply extrapolated to apply to the chronically ill human heart. But these are acute experiments, while in man chronic cardiac insufficiency develops only over a period of weeks or years. The acute experiment is a study of functional adaptation, but in man the structural adaptations are the more important ones. In applying Starling's law to chronic decompensation in man, it was assumed that with the fibers greatly overstretched, the consumption of oxygen per unit of heart muscle must be greatly increased. The decompensation was thought to be a result of the relative coronary insufficiency. However, we have shown that in dilatation in man the muscle fibers are not overstretched in the Starling sense, and therefore the consumption of oxygen per unit of heart muscle should be normal. The measurements of consumption of oxygen of the myocardium in man performed by Bing et al.[52,53] agree with this conclusion.

Summary

1. All normal human hearts have essentially the same number of myocardial fibers and myocardial nuclei. During physiologic growth the number of myocardial fibers remains constant; the fibers enlarge, but their length-to-width ratio remains constant (harmonic growth). The number of capillaries increases with growth, with one capillary per four fibers in the infant and one capillary per fiber in the adult. However, the width of the spaces of the capillary net is essentially the same for all age groups. The number of fibers and nuclei is roughly the same for the right ventricle as the left; the left ventricle is heavier than the right because its fibers are thicker. There are fewer layers of fibers in the right ventricle than in the left. It follows from this that the inner surface area of the right ventricle must be greater than for the left.

2. The average weight of the normal heart in man is about 300 gm. Through athletic exertion it can attain a weight of 500 gm. This increase is due to an extension of physiologic growth, with the fibers increasing in length and width but not increasing in number. The growth results in a larger than normal mobilizable blood volume.

3. As a result of pathologic demands for increased heart work as, for example, in hypertension, the "critical" heart weight of 500 gm. is exceeded. Increases in heart weight above the "critical" level are due to increase in the number of fibers with little further thickening. There is also an increase in capillaries, with the ratio of one capillary per fiber maintained. The coronary insufficiency that occurs with advanced hypertrophy is not principally due to a

failure of capillary supply but to the fact that with hypertrophy the growth of the coronary arteries and coronary ostia is retarded and atherosclerotic lesions of the coronary system become more frequent.

4. As a result of the coronary insufficiency a dilatation takes place. However, the Z-band to Z-band distance (i.e., the length of sarcomeres) of myocardial fibers in dilated hearts is the same as for normal hearts. In addition to longitudinal growth of the muscle fibers in dilatation there are also structural alterations in the myocardium with rearrangements of the architectural relationship among the muscle fibers. Therefore, dilatation as encountered in man is not characterized by overstretched fibers. This is true of dilatation whether due to coronary sclerosis, myocarditis or excessive hypertrophy. It is called "structural dilatation" as opposed to the "functional dilatation" of the acutely overloaded heart. There is an increased residual ventricular volume in the dilated heart, but it is not mobilizable.

5. Structural dilatation is the morphologic substrate of the decompensated heart. The cross section area of muscle capable of contracting is too small for the increased volume of the ventricle. Cardiac insufficiency results, not from overstretching of the fibers or inadequate oxygen consumption per fiber length in the Starling sense, but for strictly mechanical reasons. The unit muscle weight may produce a normal amount of energy liberated on contraction but it is no longer adequate to expel a normal stroke volume from a ventricle of these dimensions. In other words, the essence of myocardial failure is the discrepancy between the amount of energy necessary to expel a stroke volume and the amount of energy available. In these studies it has been shown that in most clinical cardiac disorders with heart failure the discrepancy can be adduced from changes in the quantitative morphology of the heart.

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A New Concept of Cardiac Failure*

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THE SARCOSOMES of the heart muscle are important enzyme-bearing organelles of microscopic and partly ultramicroscopic size. Their great number in the normal heart safeguards its ability to work steadily without prolonged rest periods.[1,2]

SARCOSOMES IN FAILING HEARTS

In conditions of severe heart failure, the main morphologic changes in the heart are expected in the sarcosomes rather than in the myofibrils.[2,3] Until recently only a theory, the suspected abnormality of the sarcosomes in cardiac failure has been finally proved by electron microscopy.[4] In ten human beings who died in chronic congestive heart failure, and in one patient with carcinoma of the liver many sarcosomes in the ventricle were in a stage of osmiophilic degeneration (Figs. 1 through 7). The material for these investigations was biopsied within less than ten minutes after the death of the patients. The changes in the sarcosomes of these failing hearts prove not only that biochemical changes of intercellular and intracellular location are responsible for the abnormal function of the heart muscle, but also that a morphologically well recognizable change in the appearance and number of the enzyme-bearing sarcosomes is involved, probably as a causative factor. The function of the enzyme system of the heart is probably interfered with in heart failure by (1) a diminished amount of sarcosomes and (2) inhibiting effects of the disintegrating products.

The osmiophilic degeneration of sarcosomes in the failing heart is by no means a unique phenomenon restricted to this organ. Other organs (lungs,[5–8] liver and kidney,[12,13] pancreas[14]) have shown similar changes under pathologic conditions.

Similar observations have been previously made in the heart muscle of guinea pigs with severe scurvy,[3] in frogs who died with standstill of the heart in strophanthin poisoning[9] and in the hearts of pigeons after phosphorus poisoning and starvation.[10] Recently Poche found in the heart muscle of phosphorus-poisoned rats and of starving rats, dark osmiophilic bodies in electron microscopic images. These bodies resemble strongly the products of osmiophilic degeneration of sarcosomes, as found in human hearts (ventricle) in cardiac failure. Especially interesting are such similar findings made by Poche in the hypertrophic human atrium in mitral stenosis.[11]

SIGNIFICANCE OF MORPHOLOGIC CHANGES

Up to now, cardiac failure has been recognized clinically only as an inability of the contractive elements of the heart to work adequately. On the basis of biochemical experiments this has been attributed to humoral intracellular and intercellular changes due to slowed circulation of blood from an accumulation of metabolites such as lactic acid and pyruvic acid. Our investigations prove that in severe cardiac failure, not only humoral changes take place, but also morphologic intracellular changes. The enzyme-bearing sarcosomes, under these circumstances, are destroyed to a great extent. The fact that the disintegrated sarcosomes are osmiophilic suggests strongly the possible lipid character of these degeneration products. Also, there is the possibility that the disintegration products of these innumerable sarcosomes finally yield the lipid material (lipids, Hueck's lipofuscin), shown by light microscopy as present in the heart under such conditions. We regard the sarcosomes as the mother substance of these lipids in the heart, and not, as had been presumed, some fat brought there via the circulation and across the capillaries. This thesis is supported by our observation that the osmiophilic bodies in our specimens appear just in those places where, in the

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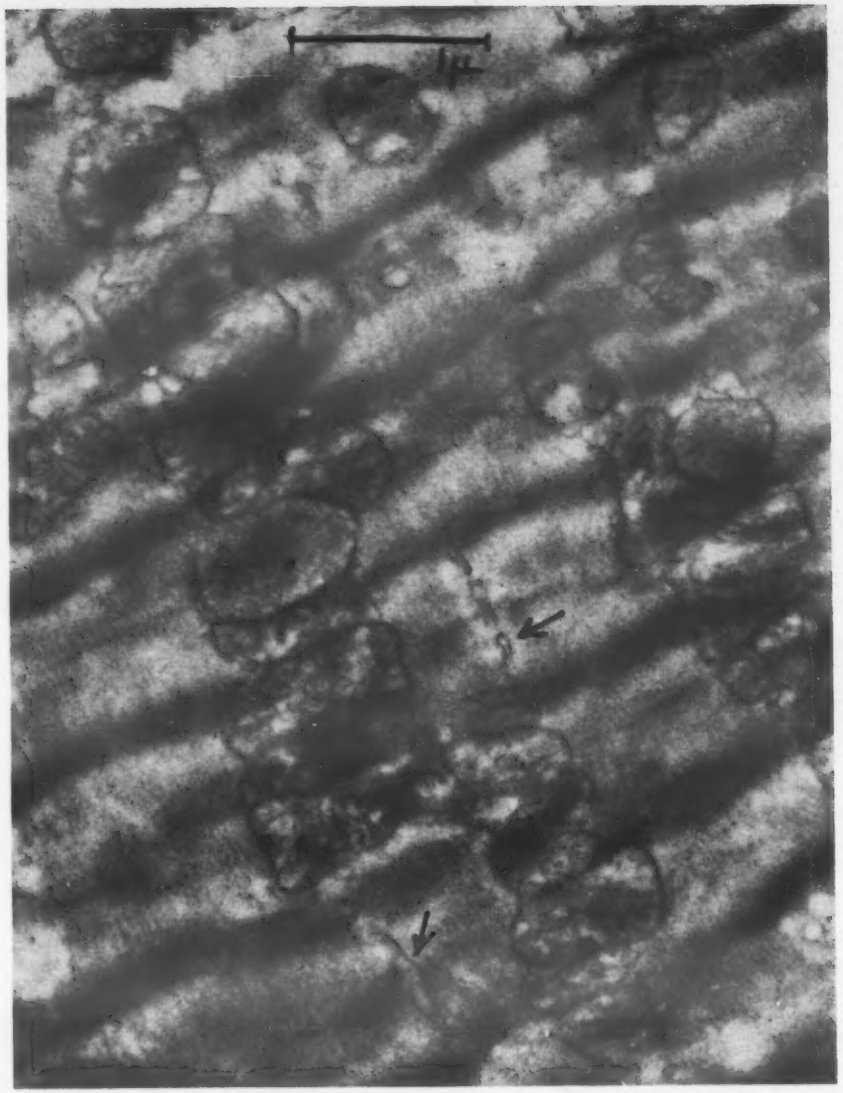

FIG. 1. Human heart (ventricle) of normal ultramicroscopic configuration. Between the striated myofibrils are rows of tightly packed sarcosomes of normal appearance. Each shows a surrounding membrane and an inner lamellar structure. Arrows indicate endoplasmic reticulum.

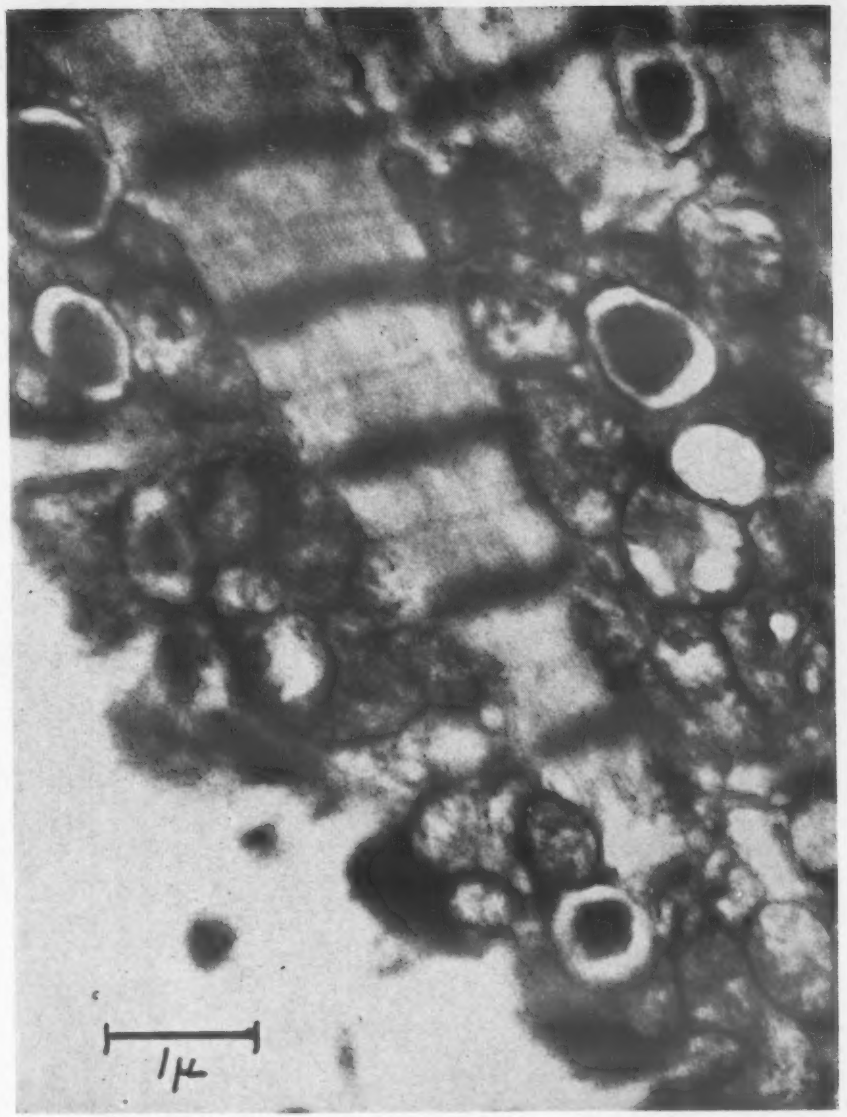

FIG. 2. Human ventricle; myofibrils and sarcosomes. Some are normal; many are in an early stage of osmiophilic degeneration. Their dark content is retracted from the surrounding membrane, which is still well recognizable.

FIG. 3. Human ventricle. Between myofibrils near nucleus (N) are many sarcosomes, some of normal configuration. Five of them (arrows) are in different stages of osmiophilic degeneration.

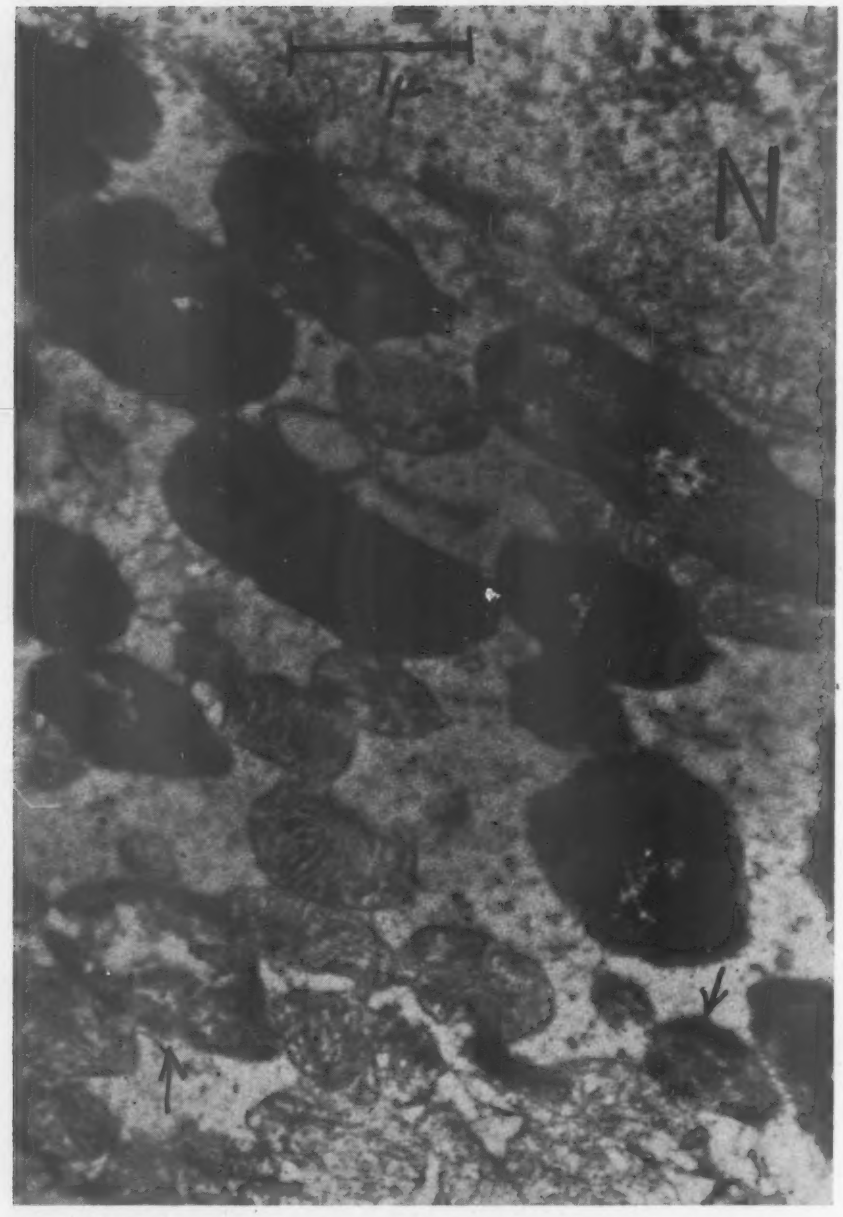

FIG. 4. Human ventricle. Near nucleus (N) are many normal and osmiophilic degenerated sarcosomes. Arrows indicate two of them in an early stage of degeneration.

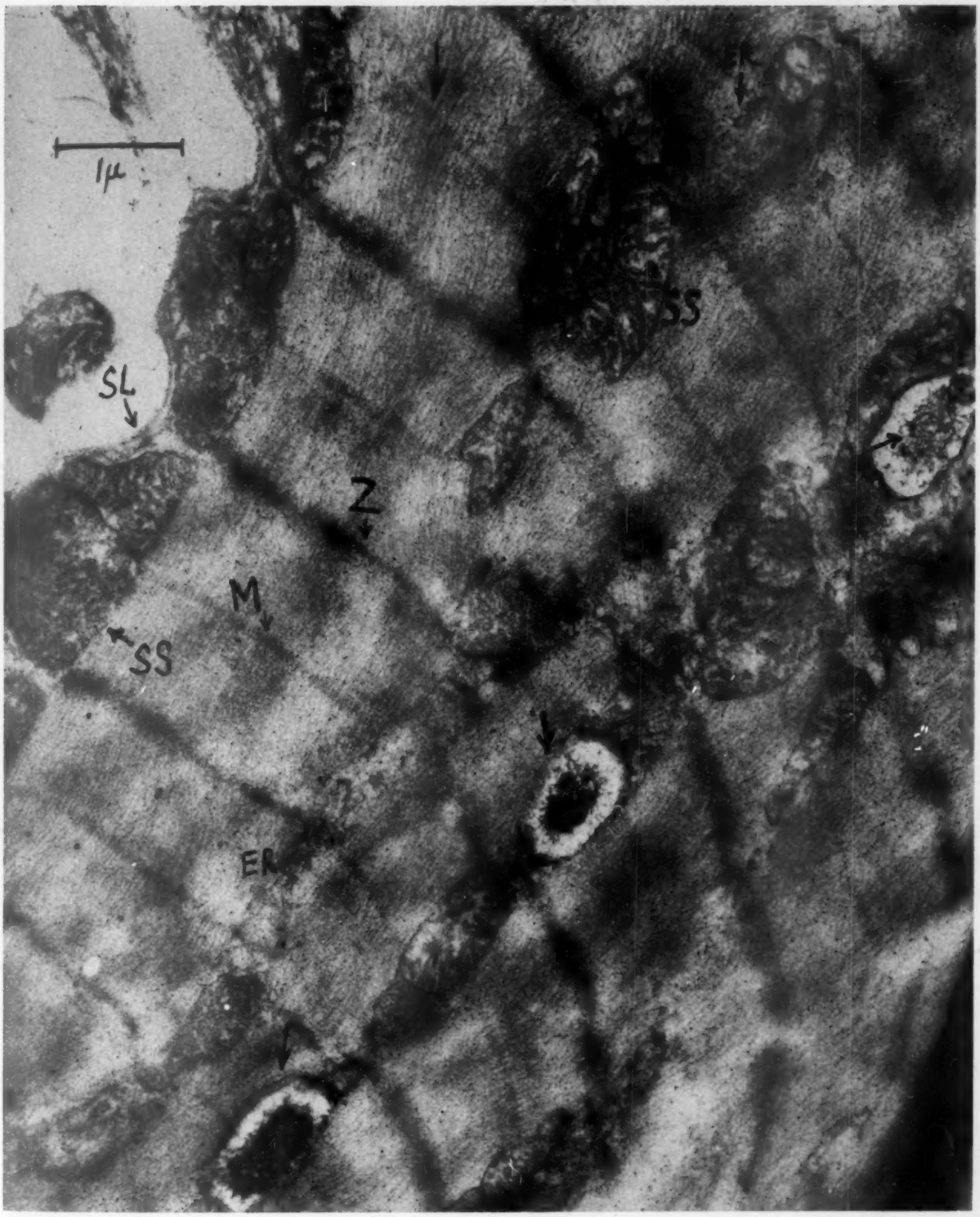

FIG. 5. Myofibrils of the human heart (ventricle). Note the typical striations of the myofibrils (Z,M). Arrow indicates a place where the M line presents only a thickening and darkening of the individual protofilaments. Between the double-lined sarcolem (SL) and the myofibril and between the different myofibrils, rows of sarcosomes (SS) can be seen, three of them, indicated by arrows, in a state of osmiophilic degeneration. ER = endoplasmic reticulum.

FIG. 6. Human ventricle. Between the myofibrils are normal sarcosomes, three osmiophilic (O) and one lameliform object. Arrows indicate early stages of osmiophilic degeneration of sarcosomes. ER is probably dilated part of the endoplasmic reticulum.

normal heart, a great accumulation of sarcosomes can be found, viz.: between the myofibrils and in the closest neighborhood of the nuclei, less often between sarcolem and myofibrils.[1,2] Poche's very similar findings in the human auricle in mitral stenosis can be explained in the same way. Digitalis intoxication, scurvy, phosphorus poisoning[14] and potassium depletion[11] damage or destroy many of the heart's sarcosomes.

This, of course, should not deny the possibility of fat droplets being deposited in the heart, as in any other organ under certain conditions. The appearance of such deposited fat droplets of ultramicroscopic dimensions differs, however, from the transformed sarcosomes in our figures.

An apparently unjustly forgotten investigation in 1916 by Scott[14] exactly confirms our recent findings and opinions on the effect of phosphorus on plasmosomes (mitochondria) as well as our findings in chronic cardiac failure. He said, "Mitochondria are the first constituents of the acinus cell of the pancreas to show pathological change in phosphorus poisoning. They lose their filamentous form, become shorter and thicker, and their bleb-like swellings which are so characteristic of the normal pancreas completely disappear. Then follows the stage of agglutination in which the mitochondria collect in large compact clumps. The mitochondria in these agglutinated masses fuse to form droplets possessing the characteristic properties of lipoid."

Sarcosomes are the mitochondria of the heart muscle.[15]

Conclusion

In summary, the following hypothesis is suggested: Most, or all, of the known diseases are conditions in which a greater part of the plasmasomes (mitochondria) of one or more tissues of the body are not working normally, due to their disorganization (swelling, disappearance of their lamellar structure, etc.), or complete disintegration (destruction of their

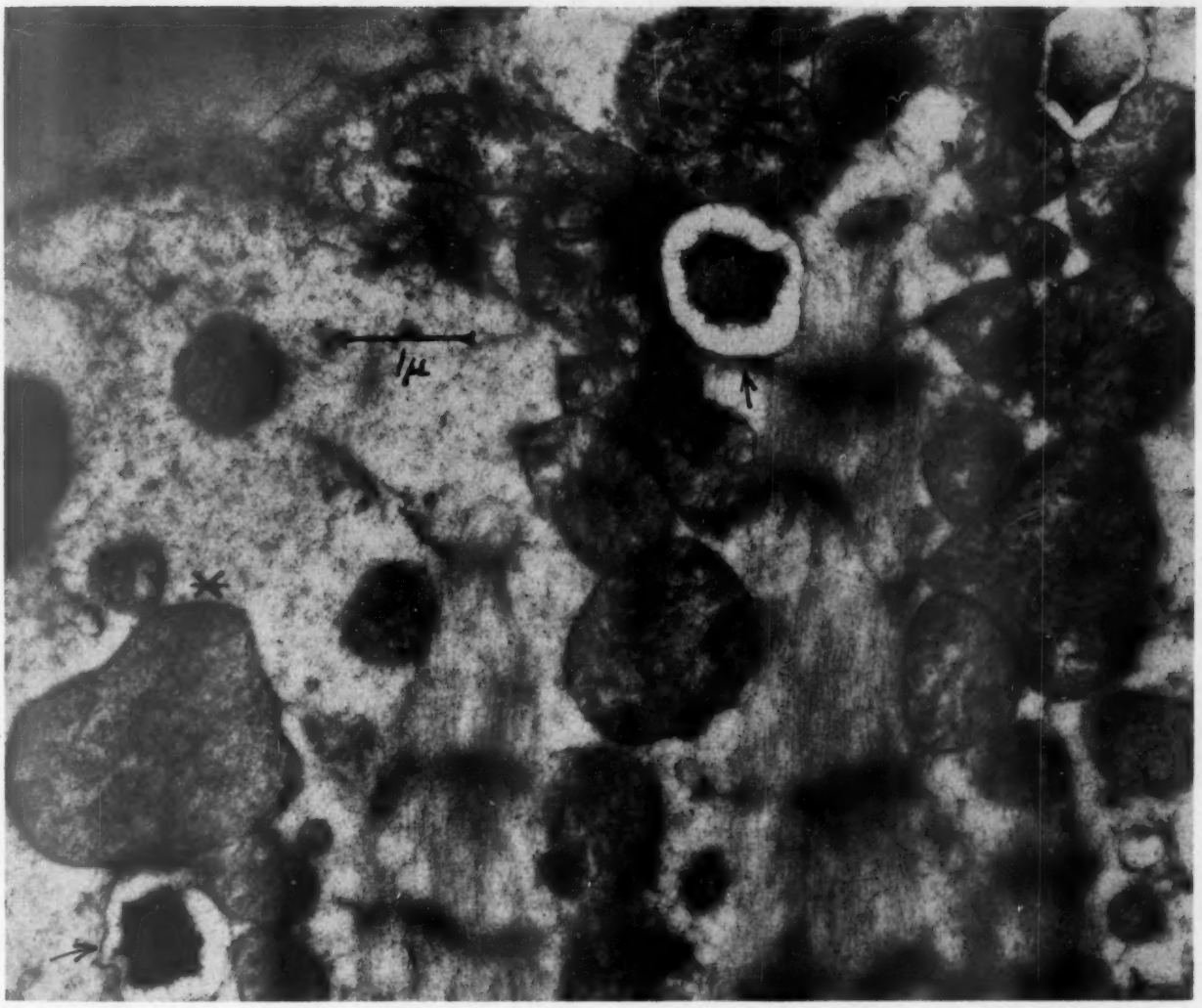

FIG. 7. Human heart (ventricle). Note the great amount of sarcosomes between the myofibrils. Some of them clearly show a normal inner lamellar structure. The large one indicated by asterisk has a nearly homogeneous content. Three of the sarcosomes are in a state of osmiophilic degeneration (arrows). The membranes of these three sarcosomes are still recognizable.

membrane, osmiophilic transformation of their contents).

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New Method

The Vectorelectrocardiogram

A Simple Method of Recording and Interpreting the Spatial Electrical Fields of the Heart*

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Spatial vectors representing the electrical fields generated in the heart can be recorded as differences in potential on standard electrocardiographic apparatus. These vector potentials are analyzed with a new and simplified method of interpretation that can be applied to any vectorcardiographic lead reference system.[1] The fundamental principles of interpretation are based on timing, direction and relative magnitudes of the recorded activation and recovery potentials.

Three-dimensional vector technics have increased diagnostic accuracy and improved clinical and pathologic correlation beyond that possible with the usual electrocardiographic methods. Nevertheless, there are many technical disadvantages inherent in the usual method of recording vector loops. Special skills and equipment are required; the method is time consuming; technically clear recordings are made with difficulty, and timing, measurement and interpretation are often cumbersome. The method of recording and interpretation described in this report retains all the experience and advantages derived from electrocardiographic and vectorcardiographic studies, and in addition simplifies recording, orientation and interpretation. It permits simple clinical diagnosis by inspection of the vector tracings.

Background

This method of spatial vector analysis assumes that the electrical activity generated in normal and diseased hearts is represented by an equivalent summation dipole, whose potential varies with time. The dipole potential, having a specific magnitude and direction, can be defined by its rectangular coordinates, X (left-right), Y (vertical) and Z (anteroposterior).

Spatial vector potentials are conventionally observed and recorded on oscilloscopic apparatus. These vector potentials are viewed as timed loops from three mutually perpendicular spatial planes: horizontal, frontal and sagittal. Each plane is derived from two of the three spatial coordinate axes: X, Y, and Z. Orientation and interpretation are simplified if each of the three spatial axes, X, Y and Z, is recorded separately on a single electrocardiographic lead. The resultant tracing has three leads which indicate clearly the timing, magnitude and direction of the electrical fields along each of the three spatial axes. This tracing has been termed a vectorelectrocardiogram because of the similarity to electrocardiographic leads. The three vectorelectrocardiographic leads, X, Y and Z, totally define electrical activation and recovery in the heart.[1]

Methods of recording the heart's electrical fields along three spatial axes have been described.[2–8] Electrodes may be placed according to Grishman,[6] Wilson,[9,10] Burger[8,11,12] and others,[8] or lead-compensating systems described by Frank,[13] Schmitt,[14] Bayley,[15] Helm,[16] Johnston,[8] Dower and Osborne[17] and others[8] may be used. Recordings can be made on simple office electrocardiographic equipment in a few minutes' time. More elaborate, multichannel,

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TABLE I

Simplified Scheme for Rapid Clinical Interpretation of Vectorelectrocardiogram

	X	Y	Z
QRS vectors			
Initial direction (10 msec.)*			
Early vectors (0.04 sec.)			
Direction			
Duration†	Right:	Superior:	Anterior:
Magnitude			
Late vectors (after 0.04 sec.)			
Direction			
Magnitude			
Terminal appendage			
Maximal vector timing‡	Right: Left:	Superior: Inferior:	Anterior: Posterior:
Maximal vector sequence§			
Slurring, notching and delayed conduction			
Mean axis			
ST and T vectors			
ST vectors			
T vectors			

* Normal = right and anterior; septal rotation = anterior and left.
† Right = 0.02 sec.; superior = 0.03 sec.; anterior = 0.04 sec.
‡ Maximal leftward = 0.05 sec.
§ Right, anterior, left, posterior.

multispeed, wide band amplifying recorders provide additional details if desired.

Advantages of this technic over the vectorcardiographic loop method are immediately apparent:

(1) It is a simple three-lead system.

(2) A complex oscillographic tube and associated multiple amplifiers and circuits are not needed.

(3) A permanent record is obtained in a form familiar to all physicians.

(4) It is readily adaptable to existing equipment with a minimum of time and expense.

(5) Accurate timing, measurement and orientation of the instantaneous vectors is simple by usual electrocardiographic methods.

(6) It is applied readily to arrhythmias and conduction disturbances.

(7) A record can be made at normal speeds or multiples thereof for resolution of small details or conduction defects.

(8) Combination of any two leads of the vectorelectrocardiogram permits visualization of the spatial vectorcardiographic loop by inspection.

(9) Interpretation and diagnosis are made by inspection.

Interpretation

In the heart the sequence of activation and recovery has a specific timing and spatial orientation.[8,18–22] Normal variations fall within a narrow range. Accurate timing allows identification of the portion of the heart muscle undergoing activation. Pathologic states are detected and localized by specific changes in timing, direction and relative magnitude of the recorded activation and recovery potentials.[8,18–23]

The time sequence and orientation of the instantaneous repolarization vectors cannot

TABLE II
Ventricular Hypertrophy

	Right Ventricular Hypertrophy	Left Ventricular Hypertrophy
QRS vectors		
Initial direction	Right and anterior	Right and anterior; left and anterior*
	Anterior and left*	
	Left and posterior*	
	Right and posterior*	
	Anterior and right*	
Early (0.04 sec.)	Increased right and anterior	Increased left and posterior
Late (after 0.04 sec.)	Right and anterior	Left and posterior†
		Maximum left >0.05 sec.
Terminal appendage	Right and anterior or right and posterior	. . .
Mean axis	. . .	Horizontal
Notching and slurring	No abnormal conduction delay	No abnormal conduction delay
Sequence of maximal vectors	raLAR	raLP
		ALP*
	raLARP (moderate)	PL (severe)‡
	ARP (severe)*	
	RP (severe)*	
	aLARP (severe)*	
	raLPRA (severe)*	
ST and T vectors	Directed away from the terminal QRS vectors	Right and anterior, away from the maximal left and posterior QRS vectors

* Septal rotation.
† Increased QRS duration (0.09 to 0.11 sec.).
‡ Questionable septal rotation.

TABLE III
Complete Bundle Branch Block

	Right Bundle Branch Block	Left Bundle Branch Block
QRS vectors		
Initial direction	Right and anterior	Left and posterior
Early	Normal or increased anterior and right	Increased left and posterior
Late	Anterior and right	Left and posterior
Terminal appendage	Anterior and right	. . .
Axis	. . .	Horizontal
Delayed conduction	During last 0.04 to 0.08 sec.	During interval between 0.04 and 0.09 sec.
QRS duration	0.12 sec. or greater	0.12 sec. or greater
Sequence of maximal vectors	raLAR	PL
ST and T vectors	Directed away from terminal QRS vectors	Directed away from maximal left and posterior QRS vectors

be used to identify the specific portion of the heart as in the activation cycle.[24] Therefore, the recorded recovery potentials must be interpreted from their spatial orientation, contour and configuration (slope) and relation to respective activation potentials.

Any method of interpretation of vector potentials must utilize known principles of electrophysiology and conduction in the heart. The method described herein retains and utilizes all the experience and advantages of present and past electrocardiographic, vectorcardiographic and direct-lead studies. Grant[22] has discussed in detail the effects of pathologic processes on activation and recovery. For the vectorelectrocardiographic method, his concepts have been extended to each instant of the cardiac cycle, rather than limiting the diagnostic criteria to an early and late mean vector.

Pathologic processes may increase or decrease the electrical fields generated in an involved region of cardiac muscle. Increase in a localized electrical field is determined by a greater than normal magnitude and duration of the recorded vector potentials; decrease in a localized electrical field is determined by reduction in magnitude or duration of these vector potentials or by a change in their direction.

An increase in magnitude or duration of the vector potentials may result from the following: (1) an absolute increase in this localized muscle mass (hypertrophy); (2) blocking or delayed conduction in this regional muscle mass; or (3) a loss of muscle mass generating opposing electri-

TABLE IV
Myocardial Infarction

QRS Vectors
Early QRS Vectors (1) Decrease or loss of normal QRS magnitude (2) Shift away from the region of necrosis (3) Abnormal duration of the early rightward, superior, or anterior QRS vectors (4) Notching and slurring
Late QRS vectors (1) Shift toward the region of necrosis (2) Notching, slurring. or delayed conduction (localized)
Sequence of Maximal Vectors (1) Abnormal
ST-T Vectors
Injury (1) ST vectors directed toward the area of injury Monophasic contour with convexity toward region of injury (2) T vector may be directed away from region of injury and ischemia
Ischemia (1) ST vector directed away from the area of ischemia Convexity directed away from T vector direction (2) T vectors directed away from region of ischemia T contour is symmetrical and peaked

cal forces (e.g., infarction of opposing muscular wall).

A reduction in magnitude or duration of the vector potentials may result from: (1) destruction of muscle in the involved region (infarction); or (2) increase in muscle mass of the opposite ventricular wall.

In this simplified method of interpretation, attention is directed to the duration and timing of each portion of the cardiac cycle, the sequence of maximal or peak QRS vectors, slowed conduction or change of direction, and to the time sequence, spatial orientation and relative magnitudes of the instantaneous vectors (Table I). For convenience the instantaneous QRS vectors are divided into initial direction, early and late phase, and terminal appendage as regards timing. Magnitude is considered in a qualitative sense for rapid clinical interpretation. It is important to include diagnostic information obtained from configuration and contour of ST and T vectors. With this method every slur, notch and change in direction and orientation appears to have electrophysiologic significance. Tables II through IV list some of the electrophysiologic criteria for right and left ventricular hypertrophy, right and left bundle branch block, ischemia, injury and myocardial infarction.* This positive electrophysiologic approach is the basis of the vectorelectrocardiographic method of interpretation.

Method

Over 2,000 subjects have been studied by routine clinical methods. Many subjects have undergone cardiac catheterization, a number have had surgical exploration and a few have been examined at necropsy. A number of spatial vector loops have been made as well. Standard electrocardiograms were recorded on all subjects.

Vectorelectrocardiograms were obtained with electrodes† placed according to: (1) the Grishman cube system,[6] (2) the Frank seven-lead compensating system,[13] and (3) the Dower and Osborne four-lead compensating system.[17] The majority of vectorelectrocardiograms were derived according to Grishman, as our experience with this method is greater. Figure 1 illustrates the electrode placements and the wiring necessary to obtain the X, Y and Z components. These components may also be recorded with standard electrocardiographic equipment through the lead I positions (right arm-left arm) and suitable switching (Fig. 2). The electrocardiographic gain control is advanced to maximum. The orientation is such that an upright deflection represents left in X lead, superior in the Y lead and anterior in the Z lead. Tracings have been recorded at 25 mm./second on direct writing apparatus. A few have been made on direct writing equipment at 50 mm./second and occasionally on the twin beam photographic recorder at 75 mm./second.

Because of low amplitude in many vectorelectrocardiograms, details of activation and recovery are often obscured within or near the base line. A direct coupled preamplifier‡ is recommended to provide additional gain over that available from the standard electrocardiographic amplifier (Fig. 3).

With a heated stylus recorder, the temperature control must be at the minimum level compatible with a clear recorded tracing. Further clarity may be obtained using an oscilloscope or photographic recording equipment with galvanometers to produce a fine line trace.

This report will present selected vectorelectrocardiographic tracings together with the correspond-

* Further discussion and more details have been submitted in a separate report.[1]

† Welsh self retaining electrodes may be used.

‡ Sanborn No. 55 Transistor or Tektronix No. 122 Preamplifier.

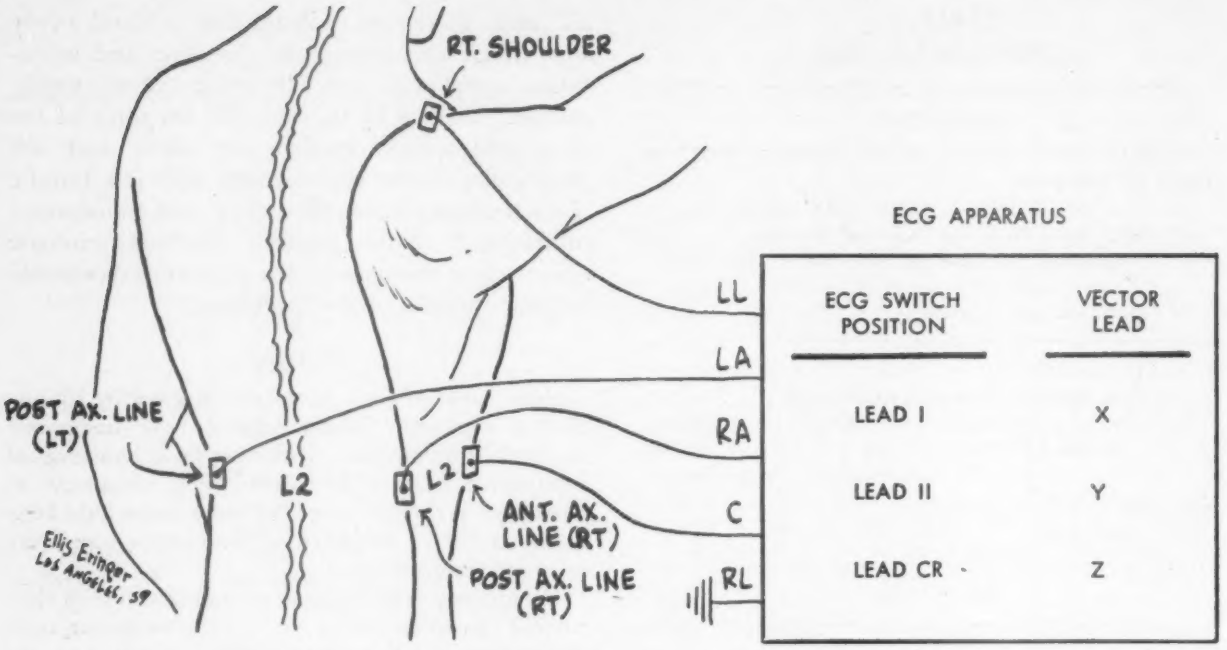

FIG. 1. Simple electrode placement and lead connections for Grishman cube reference system.

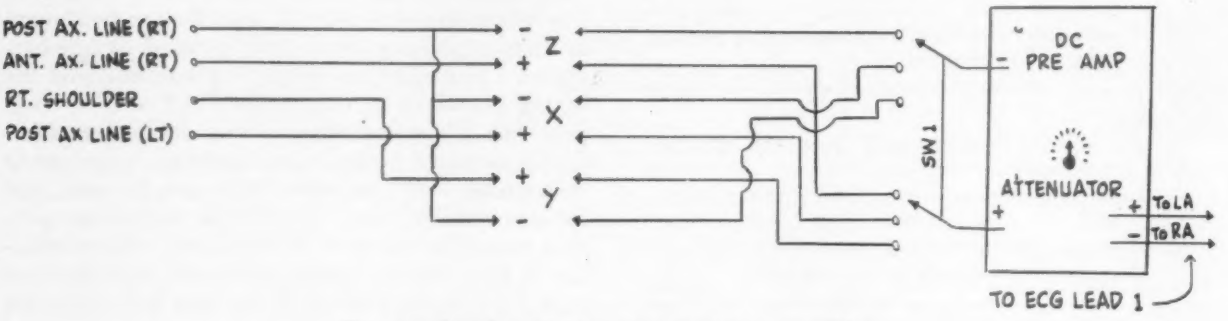

FIG. 2. Simple switching circuit with preamplifier.

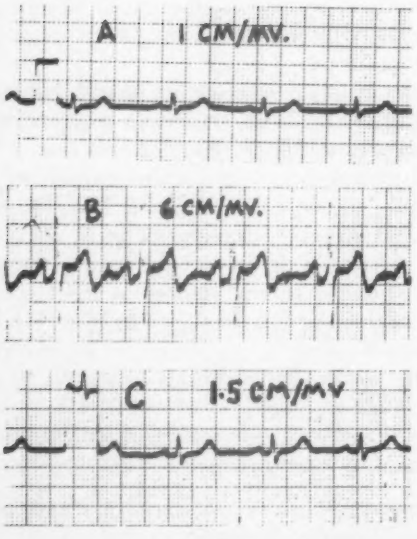

FIG. 3. Vectorelectrocardiogram. A, without preamplification. B, with preamplification at 6× gain. C, without preamplification at 1.5× gain.

ing electrocardiogram to illustrate the methods of recording and interpretation. The vectorelectrocardiograms will be analyzed in detail and correlated with the electrocardiograms.

ILLUSTRATIVE CASES

CASE 1. *Normal Subject:* C. F., a forty-eight year old woman, was a normal subject (Fig. 4). The vectorelectrocardiogram and vector loops were recorded according to the method of Grishman; the vectorelectrocardiographic sensitivity was 1.2 mv./cm.

The *electrocardiogram* is interpreted as within normal limits.

The vectorelectrocardiogram has normal right and anterior initial QRS vector directions indicating intact septal activation. The early QRS vectors after 0.02 second are left and anterior; the early right and anterior QRS vectors are respectively 0.02 and 0.04 second in duration. The late QRS vectors (after 0.04 second) are posterior and left. The sequence of maximal or peak QRS vectors in the horizontal

plane (combined X and Z leads) is right (0.01 second), anterior (0.02 second), left (0.04 second) and posterior (0.05 second). The direction and magnitude of the maximal T vectors is similar to the respective maximal left, posterior and inferior QRS vectors; the ST and T vector contours are normal. These characteristics are exactly identified in the conventional vector loops (Fig. 4C).

This vectorelectrocardiogram has been interpreted as normal because it presents (1) normal direction, magnitude and sequence of the maximal QRS vectors, (2) normal duration of the early right and anterior QRS vectors, and (3) normal direction, magnitude, contour and sequence of the ST and T vectors.

CASE 2. *Left and Right Ventricular Hypertrophy:* T. N. was a thirty-one year old woman. The vectorelectrocardiogram was recording according to Grishman with 1.3× gain (Fig. 5).

The electrocardiogram may be interpreted as showing incomplete right bundle branch block with auricular fibrillation and effect of digitalis. In addition, the tall R waves, S-T segment depression and T wave inversions in the left chest leads suggest left ventricular hypertrophy. From electrocardiographic evidence alone, it is difficult to determine whether the incomplete right bundle branch block pattern represents anatomic right ventricular hypertrophy

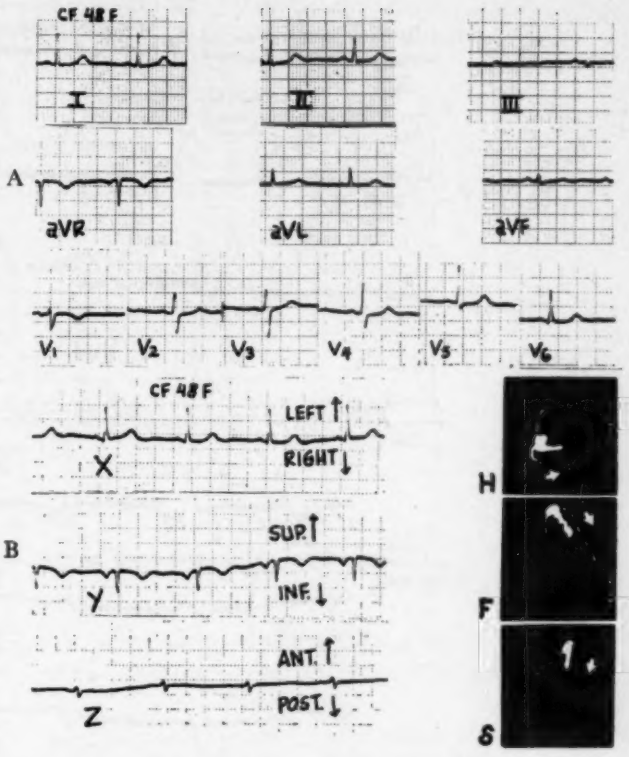

FIG. 4. Case 1. Normal electrocardiogram, vectorcardiogram and vectorelectrocardiogram.

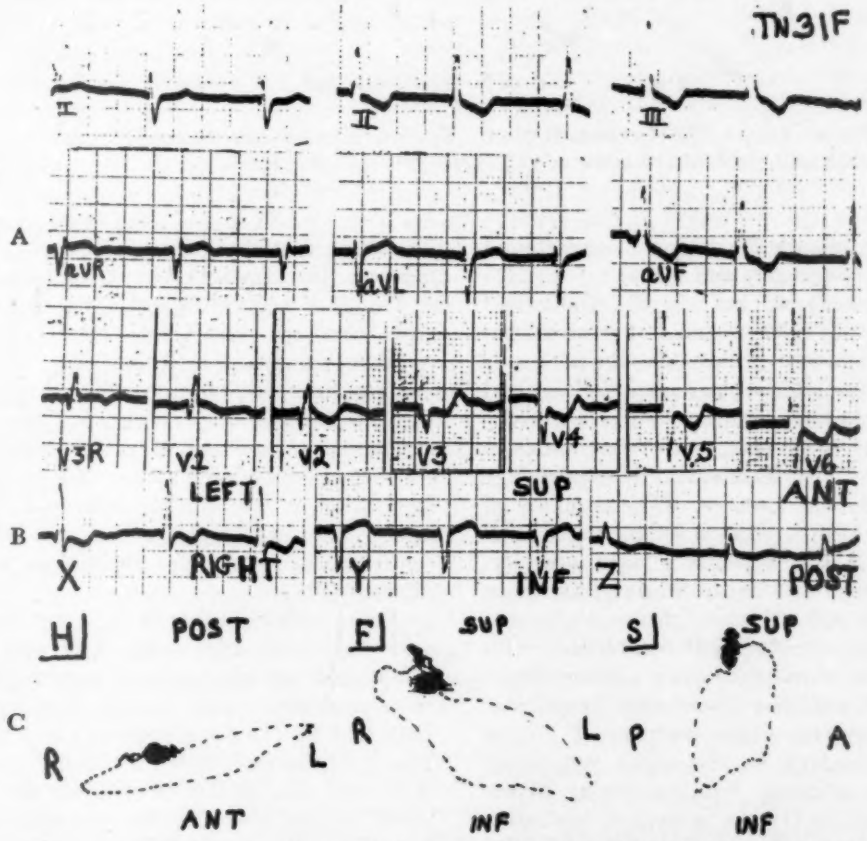

FIG. 5. Case 2. A, electrocardiogram. B, vectorelectrocardiogram 1.3× gain, Grishman electrode placement. C, vectorcardiographic loops.

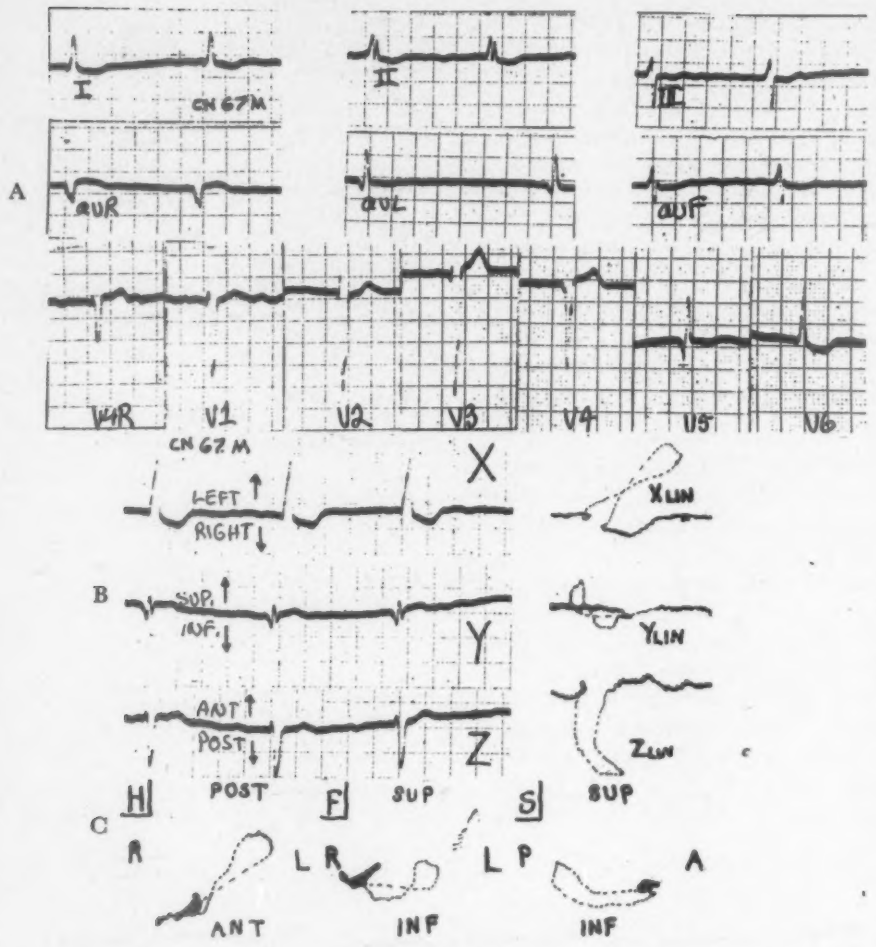

FIG. 6. Case 3. A, electrocardiogram. B, vectorelectrocardiogram 1.3× gain, Grishman electrode placement. C, vectorcardiographic loops.

alone, right bundle branch block alone, or combined right ventricular hypertrophy and block.

The vectorelectrocardiogram has normal right and anterior initial (septal) QRS vectors. The abnormal findings are as follows: Auricular fibrillation is present. The early QRS vectors after 0.02 second are left and minimally posterior, then markedly anterior. The late QRS vectors are also markedly left and anterior. The terminal QRS appendage shifts right, but remains anterior. The sequence of maximal or peak QRS vectors in the horizontal plane (combined X and Z leads) is right, anterior, posterior, left, anterior and right. This right anterior location of the late and terminal QRS vector potentials without evidence of delayed conduction, with normal initial direction and early instantaneous QRS vectors, indicates that severe right ventricular hypertrophy is present. The posterior T vector orientation is secondary to this right ventricular hypertrophy. In addition, left ventricular hypertrophy is indicated by (1) the prolonged activation time of 0.06 second for the maximal leftward QRS vector (normal 0.05 second), and (2) the right and superior orientation of the T vectors. The T vector contour also suggests effect of digitalis.

The final vectorcardiographic diagnosis is combined right and left ventricular hypertrophy, effect of digitalis and auricular fibrillation. There is no block or infarction. The postoperative diagnosis was combined atrial and ventricular septal defects.

CASE 3. *Lateral and Apical Infarction:* C. N. was a sixty-seven year old man. *The electrocardiographic* impression is myocardial infarction involving the lateral and anteroseptal regions, left ventricular hypertrophy, auricular fibrillation and effect of digitalis (Fig. 6).

The vectorelectrocardiogram indicates the initial QRS or septal vector directions, right and anterior, are intact and not abnormal as suggested by the electrocardiogram. Left ventricular hypertrophy is indicated by (1) the greater left and posterior magnitude of the early QRS vectors, (2) the prolonged activation time of 0.07 second for the maximal leftward vector, and (3) the marked right anterior location of the ST and T vectors. The ST and T vector contours also indicate effect of digitalis.

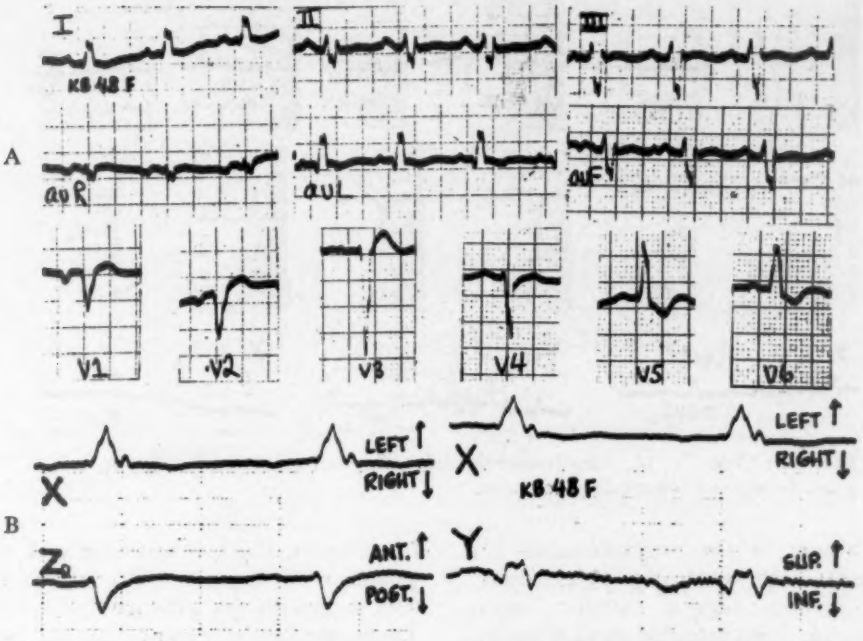

FIG. 7. Case 4. A, electrocardiogram. B, vectorelectrocardiogram 2× gain, Grishman electrode placement. Twin beam recorder, paper speed 75 mm./sec.

Slurring is present at 0.04 second in the leftward vector, not evident in the Y and Z leads. This notching represents a change in direction due to loss of leftward forces and suggests an abnormal vector is directed away from an area of infarction on the left. A horizontal position is indicated by small equiphasic complexes in lead Y (axis approximately zero degrees), suggesting the apex is at this leftward position. Anterior vectors are intact and not abnormal as suggested by the electrocardiogram. Furthermore, the sequence of maximal QRS vectors is abnormal during the mid-portion of the QRS, being right (0.01 second), anterior (0.02 second), posterior (0.06 second) and left (0.07 second). Normal maximal QRS vector sequence is right, anterior, left and posterior. Activation of the posterior muscle mass prior to the left indicates a localized delay in activation on the left. Localized blocking at 0.06 to 0.07 suggests peri-infarction block. The S-T vector contours and orientation do not indicate acute ischemia or injury; the infarction, therefore, is old or healed.

The final vectorelectrocardiographic impression is healed lateral or leftward infarction located at the apex, left ventricular hypertrophy, effect of digitalis and auricular fibrillation. There is no evidence for septal infarction. At necropsy, the heart weighed 400 gm. and there was a large aneurysm at the apex; the septum was intact.

CASE 4. *Left Ventricular Hypertrophy with Delayed Conduction Due to Myocardial Fibrosis:* K. B. was a forty-eight year old woman. *The electrocardiogram* may be interpreted as showing either severe left ventricular hypertrophy with intraventricular conduction defect or left bundle branch block, myocardial infarction and effect of digitalis. It is impossible to determine whether this electrocardiographic pattern represents an anatomic left ventricular hypertrophy, left bundle branch block, or both; nor is there clear evidence for infarction (Fig. 7).

The vectorelectrocardiogram was recorded at 75 mm./second on the twin beam recorder at 2× gain. The abnormal findings are as follows: The initial QRS vectors are left and anterior. In left bundle branch block the initial QRS vectors are always directed posteriorly. Therefore, left bundle branch block is not present. Left ventricular hypertrophy is indicated by (1) the left and anterior initial QRS vector direction, (2) the increased magnitude of the early left and posterior QRS vectors, (3) the prolonged activation time of 0.06 second for the maximal leftward QRS vector, and (4) the right and anterior ST and T vectors oriented opposite these large left and posterior QRS vectors. The maximal QRS vector sequence is left, anterior, posterior, left, and there is a small terminal appendage left and posterior. No rightward vectors are present. In complete left bundle branch block, activation of the posterior wall usually precedes the leftward maximal vector by 0.03 second or more. The very short interval of 0.005 second between the maximal posterior and leftward vectors in this tracing is further evidence against the diagnosis of left bundle branch block. Excessive slurring and notching are present in all three leads during all portions of the QRS. These notches indicate both delayed conduction and aberrant pathways throughout the myocardium (multiple changes in direction). Blocking during the initial 0.04 second interval of the

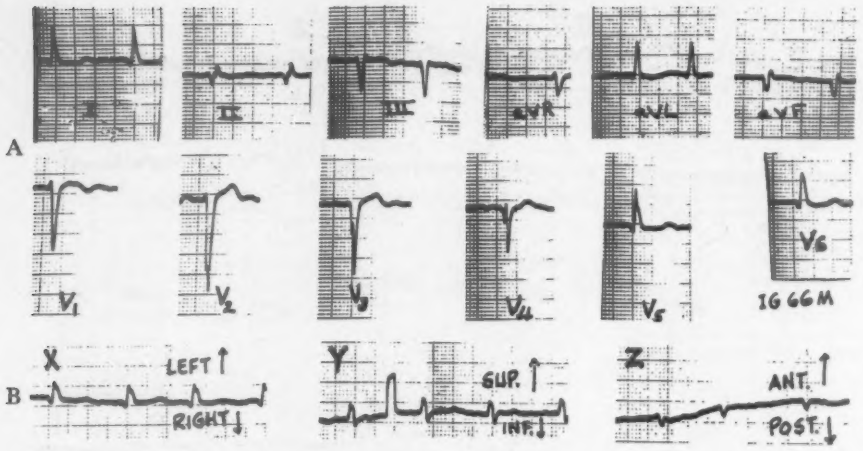

FIG. 8. Case 5. A, electrocardiogram. B, vectorelectrocardiogram 1.3× gain, Grishman electrode placement.

QRS usually is absent in the uncomplicated left bundle branch block or left ventricular hypertrophy. Therefore, these findings suggest extensive myocardial fibrosis resulting from multiple areas of healed infarction.

The final vectorelectrocardiographic diagnosis is left ventricular hypertrophy, effect of digitalis and delayed conduction throughout the ventricle due to extensive myocardial fibrosis. Left bundle branch block is not present.

CASE 5. *Myocardial Infarction, Left Ventricular Hypertrophy and Peri-Infarction Block:* I. G. was a sixty-six year old man. *The electrocardiogram* is interpreted as showing myocardial infarction involving the lateral and diaphragmatic or posterior walls, left ventricular hypertrophy and auricular fibrillation. Infarction of the free anterior wall is indicated by the diminished R waves in leads V_3 and V_4. Furthermore, the prolonged QRS duration of 0.12 second suggests either intraventricular conduction defect or left bundle branch block (Fig. 8).

The vectorelectrocardiogram was recorded according to Grishman at 1.2× gain. There is auricular fibrillation. Septal forces are intact as the initial QRS vector directions are right and anterior. Intact initial septal vectors precludes diagnosis of left bundle branch block. The early rightward QRS vectors are prolonged to 0.04 second (normal 0.02 second) indicating infarction on the left. The early superior QRS vectors are prolonged to 0.05 second (normal 0.03 second) indicating inferior or diaphragmatic infarction. The early anterior QRS vectors are present but of very small magnitude and short duration. The maximal QRS vector sequence is anterior, right, posterior and left indicating infarction of the anterior wall as suggested by the electrocardiogram. The equiphasic complexes in lead Y (axis approximately −5 to −10 degrees) indicates the heart is horizontal and suggests the apex is at the leftward position. This places the infarction at the left or lateral, anterior and inferior aspects of the apex. In addition, there is notching and slurring at 0.06 second in the superior QRS vector of lead Y and at 0.08 second in the leftward QRS vector of lead X. These notches represent changes in direction and suggest peri-infarction block at the inferior and lateral regions, respectively, of the heart. Left ventricular hypertrophy involving essentially the lateral wall is also indicated by (1) the prolonged time of 0.06 second for the maximal leftward QRS vector, and (2) the relatively normal magnitude of the posterior QRS vector.

The final vectorelectrocardiographic impression is myocardial infarction involving the anterior, lateral and diaphragmatic regions of the apex, left ventricular hypertrophy with intraventricular conduction defect probably due to peri-infarction block, and auricular fibrillation. Left bundle branch block is not evident.

CASE 6. *Right Bundle Branch Block:* L. G. was a forty-seven year old male. *The electrocardiographic findings* are characteristic of right bundle branch block (Fig. 9).

The abnormal vectorelectrocardiographic findings are as follows: The initial QRS vectors are left and anterior. Initial left and anterior QRS vector directions have been recorded in certain normal vertical hearts with clockwise rotation. The early QRS vectors are normal during the first 0.03 second. After 0.03 second, these QRS vectors shift to the right and markedly anterior. No posterior QRS vectors are evident. The early maximal anterior QRS vector occurs at 0.025 second and the leftward at 0.03 second. The late maximal anterior QRS vector occurs at 0.09 to 0.10 second and is greater in magnitude. Therefore, the sequence of activation is anterior, left, anterior and right. The late and terminal QRS vectors are right and anterior, and are slurred in all three leads indicating blocking and delayed conduction. The total QRS duration is 0.14 second. Therefore, right bundle branch block is present without right ventricular hypertrophy or infarction because (1) there are normal early activa-

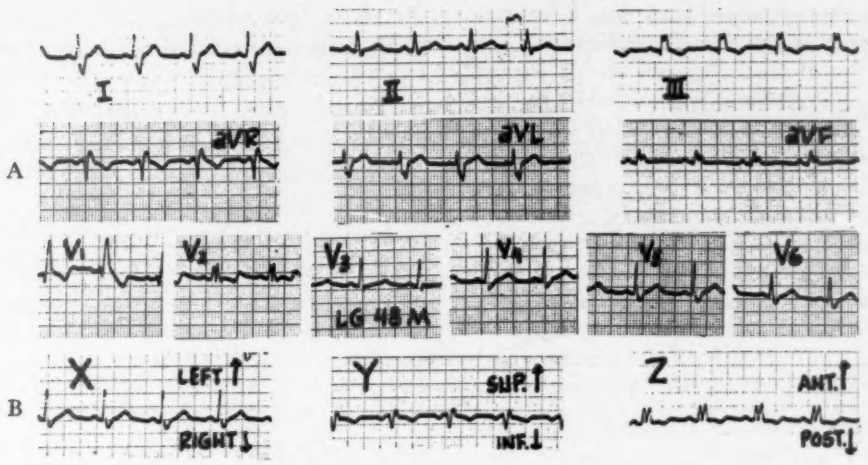

FIG. 9. Case 6. A, electrocardiogram. B, vectorelectrocardiogram 1.5× gain, Dower and Osborne compensating network.

tion forces and (2) the late and terminal QRS vectors are right and anterior with delayed conduction during the last 0.08 second of the QRS. The ST and T vectors are left and posterior, opposite the blocked terminal portion of the QRS, providing further evidence for right bundle branch block.

The final vectorelectrocardiographic impression is right bundle branch block uncomplicated by right ventricular hypertrophy or infarction. During thoracotomy for excision of a benign interlobular lipoma of the lung, the right ventricle appeared normal and no myocardial infarction was evident.

CASE 7. *Right Bundle Branch Block and Old Infarction of the Posterior Wall:* S. B. was a sixty-six year old man. *The electrocardiogram* may be interpreted as showing right bundle branch block with myocardial infarction involving the inferior or posterior wall, ischemia of the anterior and lateral walls, and epicardial injury in the region of the anterior septum (leads V_1 and V_2) (Fig. 10).

The vectorelectrocardiogram shows normal right and anterior initial QRS vectors. Septal infarction is not evident. The early QRS vectors are markedly anterior suggesting loss of the opposing forces of the posterior wall. The late and terminal QRS vectors shift to the right but remain anterior, and there is delayed conduction in all three leads during the last 0.07 second of the QRS. Total QRS duration is 0.12 second. The early maximal anterior QRS vector occurs at 0.025 second and the late anterior at 0.08 second; the maximal leftward QRS vector occurs at 0.035 second. Therefore, the sequence of maximal QRS vectors is right, anterior, left, anterior and right. This maximal vector sequence is normal during the first 0.035 to 0.04 second interval of the QRS. Normal early activation vector sequence plus prolonged blocking during late and terminal right and anterior QRS vectors indicate right bundle branch block is present. The greater than normal magnitude of the early anterior QRS vector potentials indicates loss of opposing forces of the posterior wall due to myocardial infarction of the posterior wall rather than increased right ventricular mass.

Large left and posterior ST and T vectors are common in right bundle branch block. The ST vectors

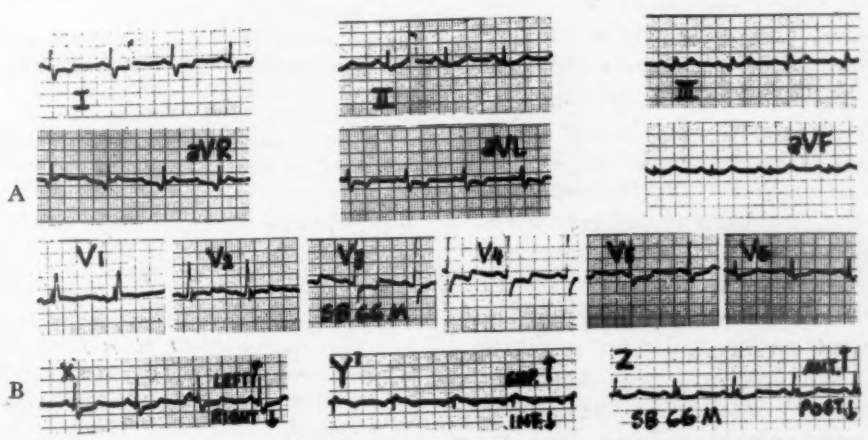

FIG. 10. Case 7. A, electrocardiogram. B, vectorcardiogram 1.5× gain, Dower and Osborne compensating network.

herein are displaced rightward, and the T vectors are anterior and of relatively small magnitude to the left. Therefore, the abnormalities of the T vector are primary and due to ischemic changes in the posterior and left (lateral) walls of the left ventricle. There is no anterior or anteroseptal injury as suggested by leads V_1 and V_2 in the electrocardiogram; this configuration probably is derived from the superior ST vector of lead Y or the rightward ST vector of lead X.

The final vectorelectrocardiographic diagnosis is right bundle branch block complicated by old infarction of the posterior wall and ischemia of the posterior and lateral walls of the left ventricle. The septum is intact.

Comments

The technic of recording the vectorelectrocardiogram is simple. It can be accomplished with any standard electrocardiographic apparatus at no additional cost. The physician may choose the vectorcardiographic method of electrode placement with which he is most familiar. A preamplifier is recommended for greater ease of interpretation. This preamplifier will provide additional gain over that available in standard electrocardiographic equipment, in order to bring out details obscured in or near the base line (Fig. 3). For even greater detail and more information on specific isolated segments of the curve, the physician may choose to record on multichannel equipment at double or greater speed. With proper technics detailed investigation of any portion of the cardiac cycle can be made.

The principles and method of interpretation have been described. Diagnosis is based on positive electrophysiologic criteria rather than empiric correlation. Particular attention has been directed to the timing and sequence of activation of the instantaneous vectors, their relative magnitudes, and their spatial orientation. This method of interpretation utilizes a direct analytic approach to the principles of electrophysiology and conduction in the heart. It retains all the experience and advantages of previous electrocardiographic and vectorcardiographic studies and simplifies recording, orientation and interpretation. Clinical diagnostic information is available by inspection; detailed mathematical analysis is also possible if desired. This method permits earlier and more accurate detection of abnormal cardiac states; anatomic localization has been excellent. These same principles and approach have been used for the interpretation of the spatial vector loops for the past few years. Table I is a suggested simplified approach for analysis of the vectorelectrocardiogram.

A large pilot study utilizing this technic is now in progress. We intend to develop a large multiphasic project with recording and analysis of data by computer technics. In addition, a direct mathematical approach to recording true individually corrected orthogonal vectorelectrocardiographic tracings from body surface leads is now being developed.

Summary

1. A simple, inexpensive and practical technic for recording the spatial vector potentials of the heart has been described. Any vectorcardiographic lead reference system can be used for recording on standard office electrocardiographic apparatus. Additional preamplification is desirable to bring out detail, and more rapid recording speeds and multichannel recording are very useful.

2. The methods, principles of analysis and illustrations of vectorelectrocardiograms are presented and described in detail. Interpretation is based on timing, spatial orientation and relative magnitudes of the instantaneous vectors. A simple, rapid clinical method of interpretation is outlined. Criteria for interpretation conforms with the basic principles of electrophysiology as derived from direct and semi-direct leads and from vectorcardiography. Correlation with known clinical and pathologic data has been excellent.

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Reports on Therapy

Hydroflumethiazide

The Clinical Pharmacology of a New Oral Diuretic*

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SINCE THE introduction of chlorothiazide, a search has continued for a benzothiadiazine compound which would be more potent from a saluretic standpoint, but which would be less likely to produce hypokalemia or other untoward effects. It would be expected that such a preparation would be effective not only as a diuretic but also as an adjunct in the treatment of hypertension.

A recently developed compound, hydroflumethiazide,† is a trifluoromethyl substituted compound (Fig. 1) which appeared to be more potent than chlorothiazide in investigation with animals.[1] Experience in the clinical pharmacology of this compound is the substance of this report.

MATERIALS AND METHODS

The approach we have used for investigation is comparable to that for other diuretics and has been described previously.[2] Six parameters were used to define the clinical pharmacology of this compound. These were the dose response curve, an estimate of the comparative potency of the preparation, the electrolyte excretion pattern, the repetitive effectiveness of the drug, its efficacy in various edematous states and its potency as an antihypertensive agent.

(*A*) *Dose Response Curve:* Ten patients with mild hypertensive cardiovascular disease, previously in congestive heart failure, but not in failure at the time of this study, were used. They were maintained under metabolically controlled conditions with a dietary sodium intake of 50 mEq. per day and 3 L. of distilled water per day. Hydroflumethiazide was given in incremental amounts beginning with 25 mg. and increasing to 100 gm. in a single dose. Each dose was repeated five times.

(*B*) *Estimate of Comparative Potency:* The significant points on a dose response curve were established as described. The optimal points were found to lie between 25 and 50 mg., and these dosages were repeated ten times each. These estimates of potency were then compared to a standard diuretic, meralluride (Mercuhydrin®), which was given a potency of "one."

(*C*) *Effects on Electrolyte Excretion:* Five patients were given 25 and 50 mg. doses of hydroflumethiazide and fractional urines were collected for twenty-four hours. These were analyzed for sodium, potassium, bicarbonate, chloride, pH and volume and were compared with control values for these patients.

(*D*) *Repetitive Effectiveness:* Five patients were given 50 mg. doses of this agent for five consecutive days. Serum electrolytes were examined before and after this period of drug therapy. The twenty-four–hour excretion pattern for sodium, potassium, chloride, bicarbonate, pH and urine volume was determined, and body weights were observed.

(*E*) *Effect of Hydroflumethiazide on Various Edematous States:* A 50 mg. dose of hydroflumethiazide was given daily for twenty-one days to twelve patients with cardiac edema, two with edema induced by steroid therapy, one with cirrhosis and edema, three with nephrotic edema and two women with edema who were in the third trimester of pregnancy. Observations were made in the control state and at the end of seven and twenty-one days on body weight, serum electrolytes, blood urea nitrogen and hematocrit.

(*F*) *Effect of the Drug as an Antihypertensive Agent:* Five patients in each of four groups were given hydroflumethiazide in a daily dose of 100 mg. daily for three weeks. The first group consisted of patients

† Hydroflumethiazide, 6-trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide, is available as Di-Ademil® from E. R. Squibb & Sons, New York, New York. It was supplied to us for this study under the name Be. 725B.

* From the Department of Medicine, Baylor University College of Medicine, and the Methodist Hospital, Houston, Texas.

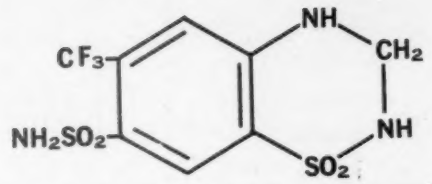

FIG. 1. Structural formula of hydroflumethiazide.

with hypertension who had been observed for three consecutive weeks prior to therapy, but who had received no previous antihypertensive therapy. The second group was composed of persons who had been receiving rauwolfia (Raudixin®, 100 mg. b.i.d.) for a period of at least three months. The next group had received rauwolfia and mecamylamine, but were inadequately controlled during a period of at least three months. The fourth group consisted of patients who had been fairly well controlled on a program of rauwolfia, mecamylamine and chlorothiazide. In this group 100 mg. of hydroflumethiazide was substituted for 500 mg. of chlorothiazide. Observations of the blood pressure response were then made at the end of the first and third weeks.

RESULTS

The results of this evaluation will be presented according to the six parameters of study.

(*A*) The significant part of the dose response curve was between the 25 and 50 mg. dose. The 100 mg. dose was not associated with an increase in sodium excretion, but did not appear to cause any evidence of clinical toxicity (Fig. 2).

(*B*) The average increase in urinary sodium at the 25 mg. dose was 84 mEq./twenty-four hours over the control values (Table I). At the 50 mg. dose the average increase was 134 mEq./twenty-four hours. These changes were paralleled by changes in urine volume and loss

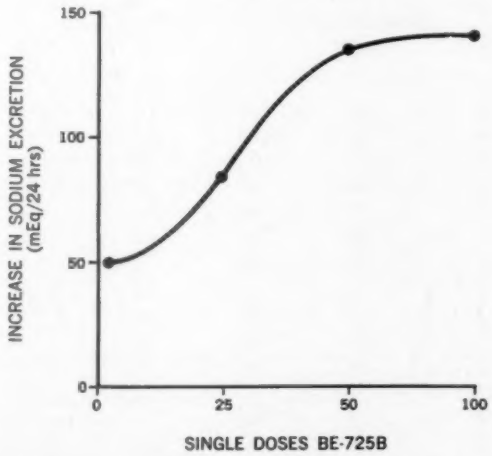

FIG. 2. Dose response curve for hydroflumethiazide. The effective dose range is shown to be between 25 and 50 mg.

TABLE I

Diuretic Responses to Single Doses of Hydroflumethiazide*

Determination	Control	Drug	Increase	"P"†
25 mg. Dose				
Urine volume (L./24 hr.)	3.0	3.5	0.5	0.01
Urine sodium (mEq./24 hr.)	47	131	84	0.001
Body weight (kg.)	56.4	55.9	−0.5	0.01
50 mg. Dose				
Urine volume (L./24 hr.	3.0	4.1	1.1	0.01
Urine sodium (mEq./24 hr.)	49	183	134	0.001
Body weight (kg.)	57.0	55.8	−1.2	0.01

* Averages of determination on 10 patients.
† "P" value derived from Student's "t" test.

of weight. Calculation of the estimation of potency revealed that hydroflumethiazide in a dose of 50 mg. per day was 1.3 times as potent as meralluride (Mercuhydrin) with the former drug being administered orally and the latter intramuscularly (Fig. 3). Expressed in a different fashion, 2 cc. of meralluride administered intramuscularly is equivalent to 40 mg. of hydroflumethiazide given orally or, 25 mg. of this drug is equivalent to 60 mg. of mercury,

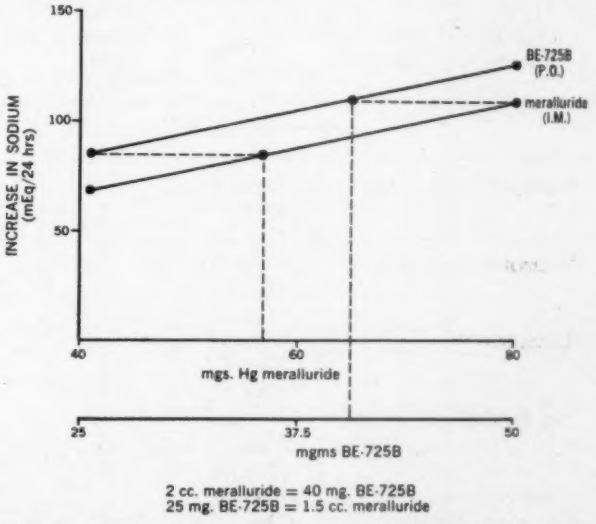

FIG. 3. Dose response curves of meralluride and hydroflumethiazide. The estimation of potency of hydroflumethiazide is 1.3 as compared to meralluride which has a potency of 1.

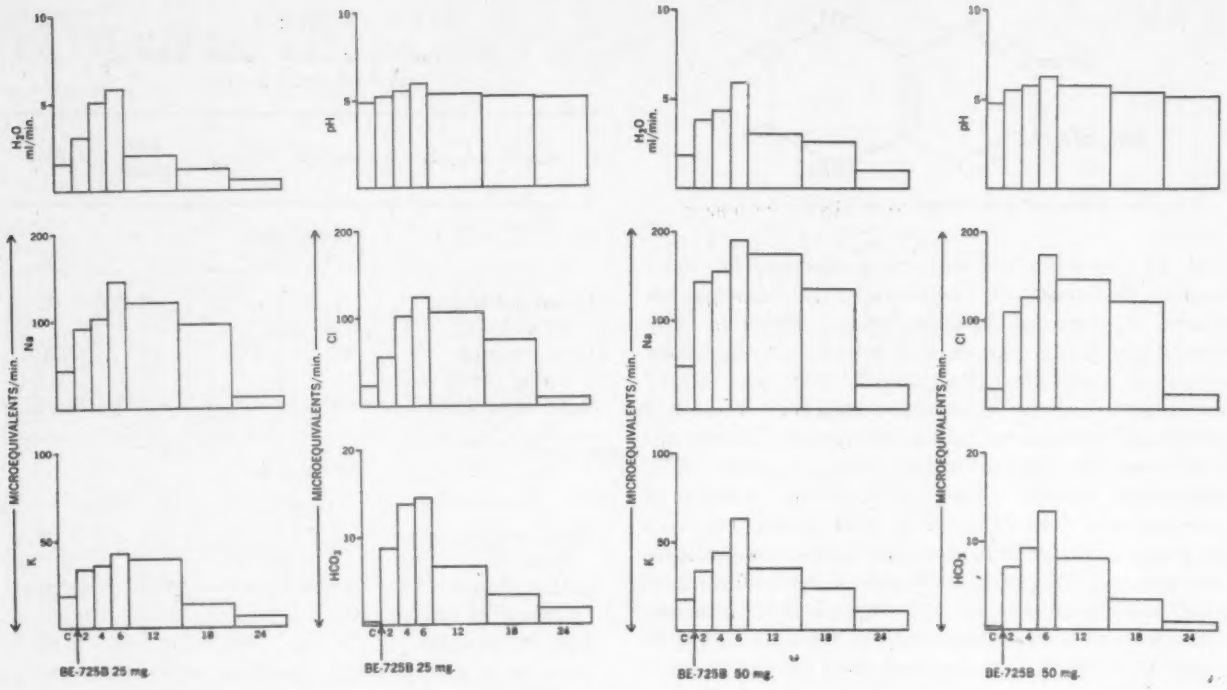

FIG. 4. Patterns of excretion following oral administration of hydroflumethiazide. *Left*, 25 mg. at 6 A.M. The composite (average of five patients) effects on electrolyte excretion reveal a predominant increase in sodium excretion and a slight increase in potassium and bicarbonate excretion. These changes are not as great as with chlorothiazide. *Right*, 50 mg. at 6 A.M. The composite (average of five patients) effects on electrolyte excretion produce no significant difference although a slightly greater sodium excretion is seen.

TABLE II

Clinical Responses to Hydroflumethiazide in Various Edematous States*
(Dose of 50 mg. Daily)

Type of Edema	No. of Patients	Period	Cumulative Weight Loss (lb.)	Serum (mEq./L.)				Blood Urea Nitrogen (mg. %)	Hematocrit (%)
				Na	K	Carbon Dioxide Combining Power	Cl		
Cardiac	12	Control	...	141	4.3	28	106	19	43
		Day 7	5	137	4.1	30	104	20	45
		Day 21	10	137	4.1	31	103	22	46
"Steroid"	2	Control	...	145	3.4	31	91	13	41
		Day 7	2	143	3.2	33	88	14	42
		Day 21	6	143	2.9	34	86	16	43
Cirrhotic	1	Control	...	130	3.0	23	86	8	38
		Day 7	6	128	2.4	22	85	10	41
		Day 21	15	127	2.4	24	83	10	40
Nephrotic	3	Control	...	129	3.5	23	92	31	39
		Day 7	5	126	3.3	24	91	28	41
		Day 21	14	124	3.3	24	88	26	42
Pregnancy	2	Control	...	143	4.1	29	103	9	38
		Day 7	2	141	3.9	31	102	10	40
		Day 21	4	140	3.9	32	101	12	41

* Average values for each group.

contained in approximately 1.5 cc of meralluride.

(*C*) There is a primary increase in sodium excretion (Fig. 4) which reaches its peak at the end of six to twelve hours and has a duration of at least eighteen hours. There is a slight increase in potassium and bicarbonate excretion (and pH also) but these changes are not as great as those seen with chlorothiazide. There was no significant difference in the electrolyte excretion pattern seen at the two dose levels, although perhaps a greater sodium excretion was seen at the 50 mg. dose.

(*D*) There is a continuous excretion of sodium following daily administration of hydroflumethiazide until depletion of excessive body stores occurs. No significant change in serum electrolytes was noted. This supports the repetitive effectiveness of this agent (Fig. 5).

(*E*) The efficacy of hydroflumethiazide in the various entities associated with edema is indicated in Table II. There was no significant change in the electrolyte pattern except the tendency toward hypokalemia in one patient with cirrhosis.

(*F*) The value of hydroflumethiazide both singly and in combination with other agents in the treatment of hypertension is shown in Table III. Although the size of each group is small the trend seems constant and the results are statistically significant.

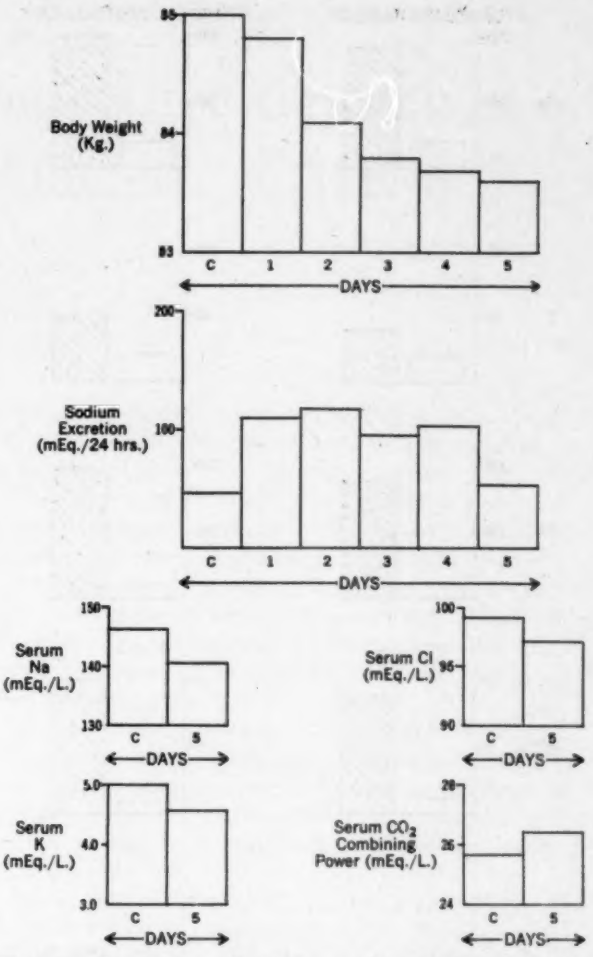

FIG. 5. Repetitive effectiveness of hydroflumethiazide (50 mg. dose) given to five patients with mild to moderate edema. There is a continuing excretion of sodium following daily therapy until there is a depletion of excessive body stores of sodium. No significant changes in serum electrolytes are observed.

COMMENTS

Hydroflumethiazide, the trifluoromethyl derivative of benzothiadiazine, appears to be a more

TABLE III

The Effect of Hydroflumethiazide as an Antihypertensive Agent*

Antihypertensive Regimen in the "Control" State	Blood Pressures in Upright Position										
	Control			After Addition of Hydroflumethiazide (100 mg. daily)							
				First Week				Third Week			
	Systolic	Diastolic	Mean†	Systolic	Diastolic	Mean†	"P"‡	Systolic	Diastolic	Mean†	"P"‡
None	195	122	146	164	110	128	0.05	150	98	115	0.001
Rauwolfia alone (Raudixin 100 mg. twice daily)	180	116	137	147	96	113	0.05	134	90	101	0.001
Rauwolfia plus mecamylamine in ganglionic blocking doses	156	108	124	128	80	96	0.05	116	74	88	0.001
Rauwolfia plus mecamylamine and chlorothiazide (500 mg. daily) (hydroflumethiazide replacement for chlorothiazide in a dose of 100 mg. daily)	138	92	107	138	90	106	N. S.	137	90	106	N. S.

* Average values for five patients in each group. † Diastolic plus one-third the pulse pressure. ‡ "P" values derived from Student's "t" test.

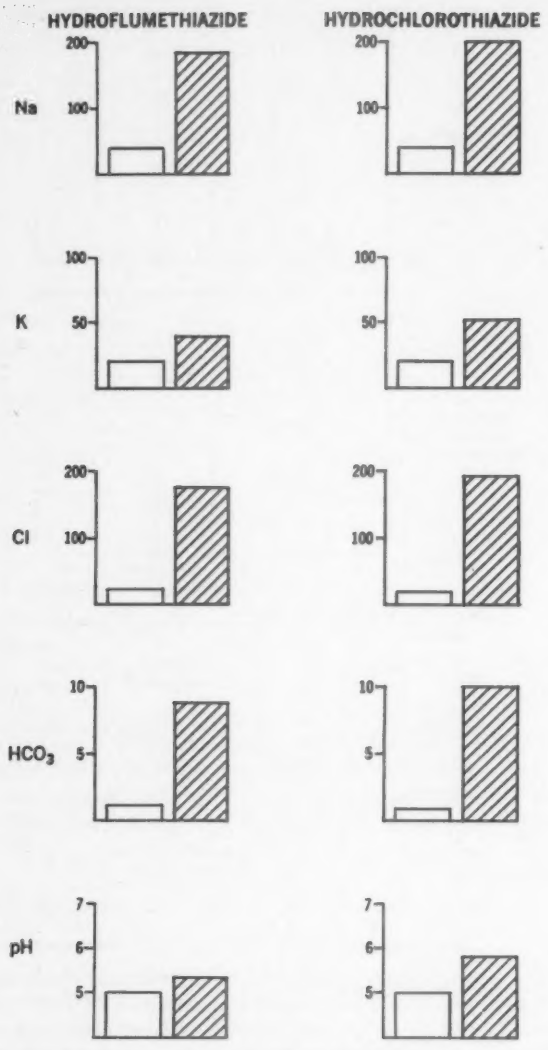

FIG. 6. Comparative effects on electrolyte excretion following two benzothiadiazine diuretics (50 mg. doses). In comparison with hydrochlorothiazide there appears to be less of a kaluretic effect with hydroflumethiazide as well as less of a loss of bicarbonate and less change in pH. (All values are reported in mEq./twenty-four hours.)

potent oral diuretic than chlorothiazide on a milligram for milligram basis. On comparison of hydroflumethiazide with hydrochlorothiazide, there appears to be a lesser tendency to hypokalemia, and a smaller excretion of bicarbonate with hydroflumethiazide. There is, therefore, a smaller change in pH (Fig. 6). In usual clinical dosage, hydroflumethiazide given orally is more effective than parenterally administered meralluride (Table IV). The drug is repetitively effective and is associated with no significant change in serum electrolyte structure. It is of value in the management of hypertension.

TABLE IV
Comparison of Potency of Various Diuretic Agents

Drug	Route of Administration	Estimation of Potency*
Hydrochlorothiazide (Hydrodiuril®)	Oral	1.4
Hydroflumethiazide (Di-Ademil®)	Oral	1.3
	Intramuscular	1.0
Meralluride (Mercuhydrin)	Oral	0.8
Chlorothiazide (Diuril®)	Oral	0.7
Flumethiazide (Ademol®)		0.5
Mercaptomerin (Thiomerin®)	Intramuscular	0.5
Chloromerodrin (Neohydrin®)	Oral	0.25
Acetazolamide (Diamox®)	Oral	

* Determined from previous analysis of variance of these drugs.

CONCLUSIONS

Hydroflumethiazide has been studied in a group of patients to evaluate the optimal dose, comparative potency, repetitive effectiveness, and clinical use in a variety of disease entities. An oral dose of 50 mg. per day appears more effective in diuretic efficacy than 2 cc. of meralluride parenterally. It acts primarily as a saluretic agent and is less likely to produce hypokalemia than chlorothiazide. It is effective in the treatment of edematous states of varied etiology, and as an adjunct in the management of hypertension.

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2. FORD, R. V., MOYER, J. H. and SPURR, C. L. Clinical and laboratory observations on chlorothiazide (Diuril). *Arch. Int. Med.*, 100: 582, 1957.

The Clinical Pharmacologic Investigation of a New Benzothiadiazine Diuretic, CMR-807*

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THE SIGNIFICANT therapeutic advance represented by chlorothiazide has prompted attempts to improve on the parent compound. The best compounds from the experimental pharmacology laboratory should be clinically evaluated to determine their value.

A clinical pharmacologic investigation of CMR-807,† a new benzothiadiazine diuretic was undertaken to evaluate preliminary experimental reports that this agent has a greater saluretic potency and a more favorable sodium to potassium excretion ratio than chlorothiazide and hydrochlorothiazide.[1] The clinical effectiveness of CMR-807 in edematous states and as an antihypertensive agent was also determined.

The chemical structure of CMR-807 is shown in Figure 1.

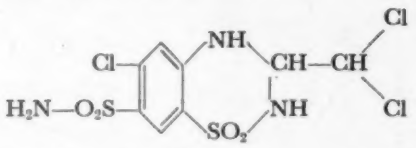

FIG. 1.

MATERIALS AND METHODS

The technics used in this study were the same as those described previously for investigation of experimental diuretics.[2] The principal aspects of the clinical pharmacology of CMR-807 were determined as follows.

Dose-Response Curve: Ten patients with mild hypertensive cardiovascular disease, who were not in failure at the time of study but had previously demonstrated evidence of edema, were used for this portion of the study. They were maintained under metabolically controlled conditions (dietary sodium, 50 mEq./day and 3 L. distilled water/day). The drug was given in incremental amounts beginning with 1 mg. and extending to 16 mg. as a single dose at appropriate intervals. Each dose was repeated five times.

Determination of Potency: The significant points of the dose-response curve were established for CMR-807 and, since these points were found to be between 4 and 8 mg., these doses were administered ten times each. Statistical analysis and computation resulted in a "potency estimation." A standard diuretic, meralluride, was given a potency of "one" for purposes of comparison.

Effects on Electrolyte Excretion: Five different patients were given 4 and 8 mg. dosages of the drug, and fractional urine samples were collected throughout a twenty-four–hour period. These were analyzed for sodium, potassium, bicarbonate and chloride levels, pH and volume.

Repetitive Effectiveness of the Drug as a Diuretic Agent and Its Influences on Serum Electrolytes: Five patients were given CMR-807 in a dose of 8 mg. daily for five consecutive days. Serum electrolytes were analyzed in the control state and after completion of drug administration. The urine was collected daily for determination of sodium excretion and volume. Body weights also were determined.

Effect of the Drug as an Antihypertensive Agent: Four groups of five patients each were given a daily dose of 8 mg. CMR-807 for three weeks. The first group consisted of patients with hypertension who had been observed for three consecutive weeks prior to therapy. The second group consisted of patients who were receiving whole-root rauwolfia (100 mg. twice daily) for a period in excess of three months. The third group comprised patients who had been receiving rauwolfia in addition to ganglionic blocking doses of mecamylamine but in whom less than optimum control had been observed for a period in excess of three months. The fourth group consisted of patients who had been fairly well controlled on a regimen consisting of rauwolfia, mecamylamine and hydrochlorothiazide 50 mg. daily. In this group, CMR-807 was substituted for the previous hydrochlorothiazide therapy in a daily dose of 8 mg. Observations were made at the end of the first and third week.

† CMR-807 is the experimental number for Naqua® (3-dichloromethyl-6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide), manufactured by the Schering Corporation, Bloomfield, New Jersey.

* From the Department of Medicine, Baylor University College of Medicine, Houston, Texas.

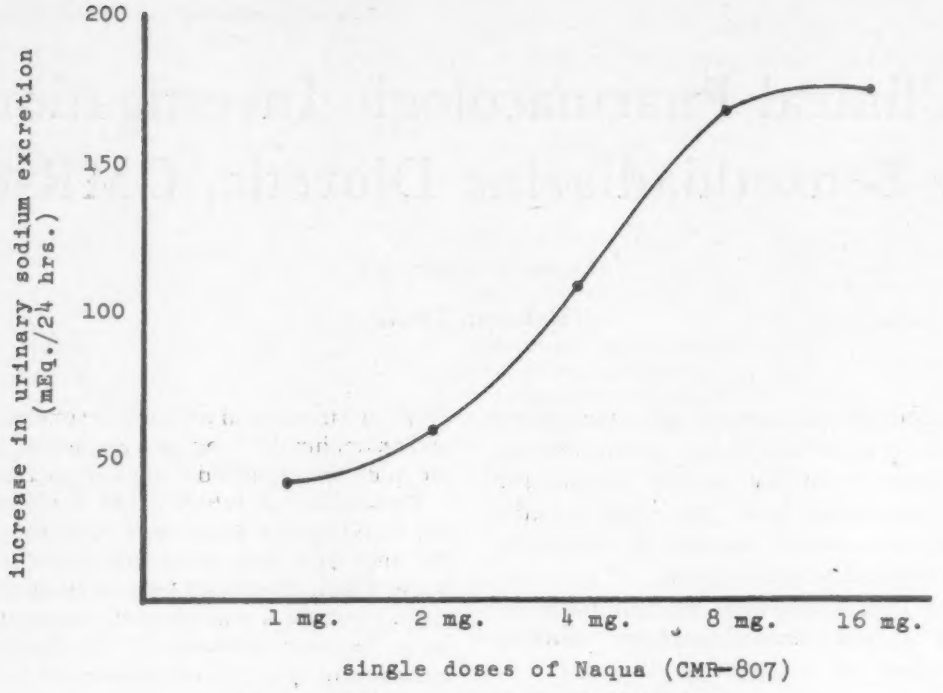

FIG. 2. Dose response curve for CMR-807.

Effect of the Drug in Various Edematous States: CMR-807 in a dose of 8 mg. daily was given for twenty-one days to ten patients with cardiac edema, two patients with cirrhotic edema, two with nephrotic edema, two with edema induced by steroid therapy and two women with a moderate premenstrual syndrome. Body weight, serum electrolytes, blood urea nitrogen and hematocrit were recorded in the control state and at the end of seven and twenty-one days. In all patients except the two with premenstrual syndromes, the therapy in the "control" state was 50 mg. hydrochlorothiazide. Two patients similar to those men-

TABLE I

Diuretic Responses to Single Doses of CMR-807
(Averages of Determinations on Ten Patients)

Determination	Control	Drug	Increase*	"P"†
4 mg.				
Urine sodium (mEq./24 hr.)	44	150	106	0.001
Urine potassium (mEq./24 hr.)	33	54	21	0.05
Urine volume (L./24 hr.)	2.9	3.6	0.7	0.01
Body weight (kg.)	67.1	66.3	−0.8	0.1
8 mg.				
Urine sodium (mEq./24 hr.)	47	215	168	0.001
Urine potassium (mEq./24 hr.)	35	63	28	0.05
Urine volume (L./24 hr.)	3.0	4.0	1.0	0.01
Body weight (kg.)	69.3	68.0	−1.3	0.1

* Increase in urinary sodium, potassium and volume, and decrease in body weight.

† "P" value derived from Student's "t" test.

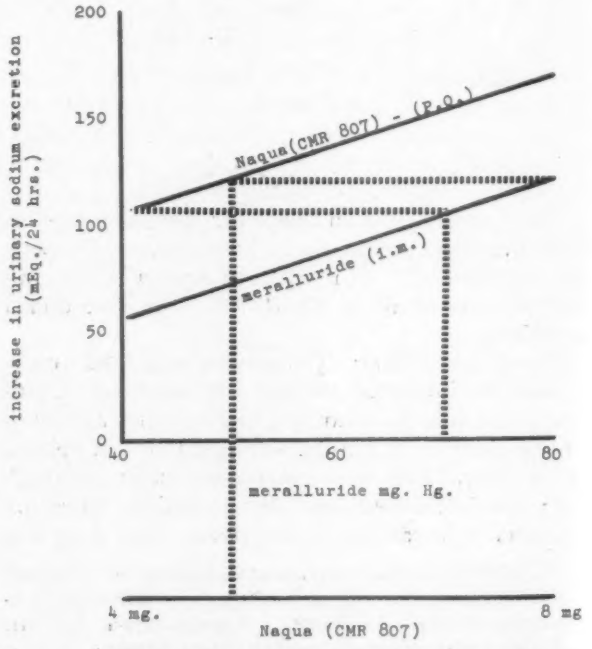

FIG. 3. Comparative potency of CMR-807 and meralluride. Two cc. of meralluride = 5 mg. CMR-807; 4 mg. CMR-807 = 1.75 cc. meralluride.

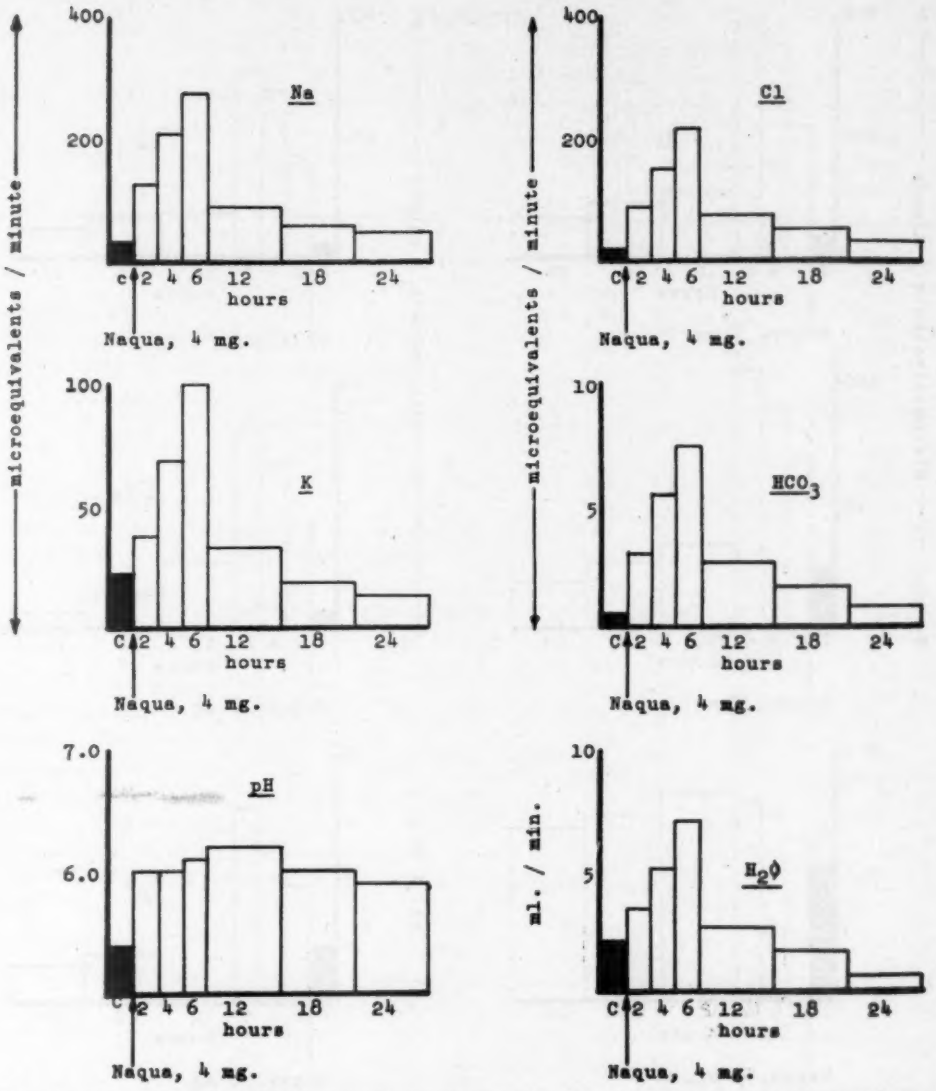

FIG. 4. Composite electrolyte excretion pattern following administration of 4 mg. CMR-807 at 6 A.M. (average values for five patients).

tioned in the section on "dose-response curve" were studied under metabolically controlled conditions and twenty-four–hour urine samples were analyzed for sodium and potassium over a twenty-one–day period. The dietary intake was 50 mEq. sodium and 40 mEq. potassium. A 4 mg. daily dose of the drug was given.

RESULTS

Dose-Response Curve: The significant part of the dose-response curve was between the 4 and 8 mg. dose level (Fig. 2). The 16 mg. dose was not associated with any further increase in sodium excretion, and, further, this dose was not associated with any evidences of clinical toxicity.

Determination of Potency: The average increase in urinary sodium at the 4 mg. dose level was 106 mEq./twenty-four hours over the control (Table I). At the 8 mg. dose level the average increase was 168 mEq./twenty-four hours. These changes, of course, were paralleled by changes in urinary volume and weight loss. Calculation of the potency estimation revealed that CMR-807 orally is 1.7 times as potent as meralluride administered intramuscularly (Fig. 3). Expressed in a different fashion, 4 mg. CMR-807 orally is equivalent to approximately 1.75 ml. meralluride intramuscularly (70 mg. Hg) since 2 ml. of meralluride is equivalent to 5 mg. of the drug administered orally.

Effects on Electrolyte Excretion: It was observed that there is a predominant increase in sodium excretion with CMR-807 which appears within two hours after administration, reaches its peak at the end of six hours, and has a duration of more than twenty-four hours (Figs. 4 and 5).

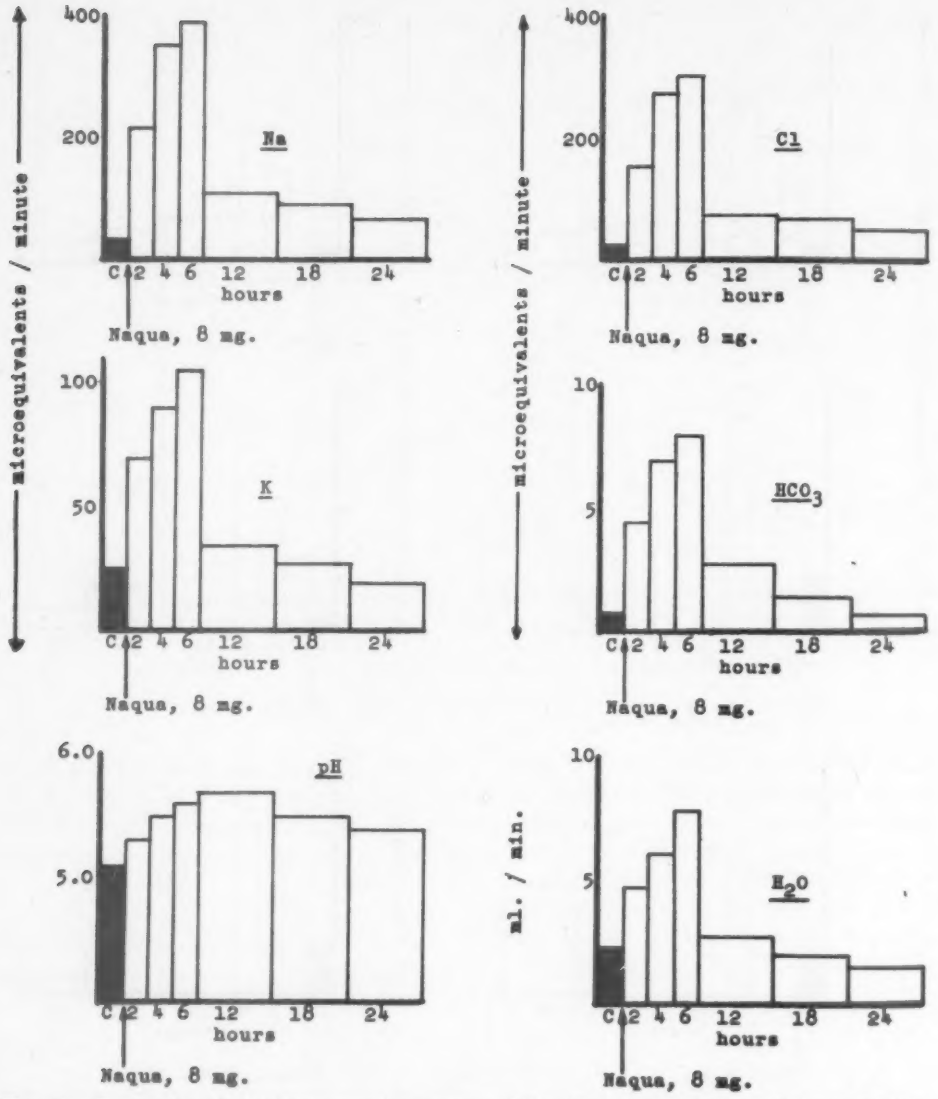

FIG. 5. Composite electrolyte excretion pattern following administration of 8 mg. CMR-807 at 6 A.M. (average values for five patients).

A slight increase in potassium and bicarbonate excretion (and pH) is seen, but these changes are not as great as those seen with chlorothiazide. There was no significant difference in electrolyte excretion patterns seen at the 4 and 8 mg. dose levels, although there was perhaps a greater sodium excretion seen with the 8 mg. dose.

Repetitive Effectiveness as a Diuretic Agent and Influence of Serum Electrolytes: There is a continuing excretion of sodium following repetitive daily therapy until depletion of excessive body stores of sodium occurs (Fig. 6). No significant changes in serum electrolytes were observed.

Effect as an Antihypertensive Agent: The drug is effective alone or in combination with rauwolfia alkaloids and ganglionic blocking agents in the treatment of hypertension (Table II). The response obtained in these patients with CMR-807 would indicate that this agent could replace other diuretics with great efficacy, but it cannot be stated whether it is more effective than hydrochlorothiazide.

Effect in Various Edematous States: CMR-807 was effective in maintaining control in various edematous states, regardless of etiology (Table III). No significant changes in the serum electrolytes or evidence of toxicity or diminished effectiveness with repetitive use were observed. It would appear that this new drug possesses distinct advantages over other diuretics in the treatment of edema, including the control agent, hydrochlorothiazide. An additional point demonstrating this was obtained in two patients studied under metabolically controlled conditions for twenty-one days. This revealed sodium

TABLE II
The Effect of CMR-807 as an Antihypertensive Agent*
(Average Values for Five Patients in Each Group)

Antihypertensive Regimen in the "Control" State	Systolic	Diastolic	Mean Blood Pressure†	"P"‡
Control				
None	212	120	151	..
Rauwolfia 100 mg. twice a day	178	108	131	..
Rauwolfia plus mecamylamine (ganglionic blocking doses)	152	104	120	..
Rauwolfia, mecamylamine and hydrochlorothiazide§	160	86	111	..
One Week after Administration of 8 mg. Daily				
None	204	110	141	N.S.¶
Rauwolfia 100 mg. twice a day	176	100	125	N.S.
Rauwolfia plus mecamylamine (ganglionic blocking doses)	144	92	109	N.S.
Rauwolfia, mecamylamine and hydrochlorothiazide§	158	88	111	N.S.
Three Weeks after Administration of 8 mg. Daily				
None	196	98	131	0.01
Rauwolfia 100 mg. twice a day	162	86	111	0.01
Rauwolfia plus mecamylamine (ganglionic blocking doses)	136	86	103	0.01
Rauwolfia, mecamylamine and hydrochlorothiazide§	160	86	111	N.S.

* Blood pressure values are recorded in the upright position.
† Diastolic plus one-third the pulse pressure.
‡ "P" values determined by Student's "t" test.
§ CMR-807 was a replacement for 50 mg. daily dose of hydrochlorothiazide.
¶ Not significant.

TABLE III
Clinical Responses to CMR-807 in Various Edematous States*
(Average Values for Each Group)

Type of Edema	No. of Patients	Period	Cumulative Weight Loss (lb.)	Serum Electrolytes (mEq./L.)				Blood Urea Nitrogen (mg. %)	Hematocrit (%)
				Na	K	CO_2 Content	Cl		
Cardiac	10	Control†	..	146	4.2	24	102	19	44
		Day 7	2	143	4.1	25	99	19	45
		Day 21	5	143	4.2	26	97	20	47
"Steroid"	2	Control	..	146	4.3	27	107	11	47
		Day 7	0	146	4.3	28	106	11	48
		Day 21	1	145	4.2	28	106	11	49
Cirrhotic	2	Control	..	138	3.8	27	96	16	44
		Day 7	0	137	3.8	27	95	16	44
		Day 21	1	138	3.9	27	94	16	45
Nephrotic	2	Control	..	141	4.1	25	109	28	42
		Day 7	0	140	4.1	26	109	29	43
		Day 21	0	140	4.1	27	109	29	43
Premenstrual	2	Control	..	144	4.3	24	111	10	42
		Day 7	3	143	4.5	25	109	11	43
		Day 21	3	143	4.4	24	110	10	42

* Dose of 8 mg. daily.
† Previous therapy with hydrochlorothiazide 50 mg. daily except in patients with premenstrual edema who had no previous therapy.

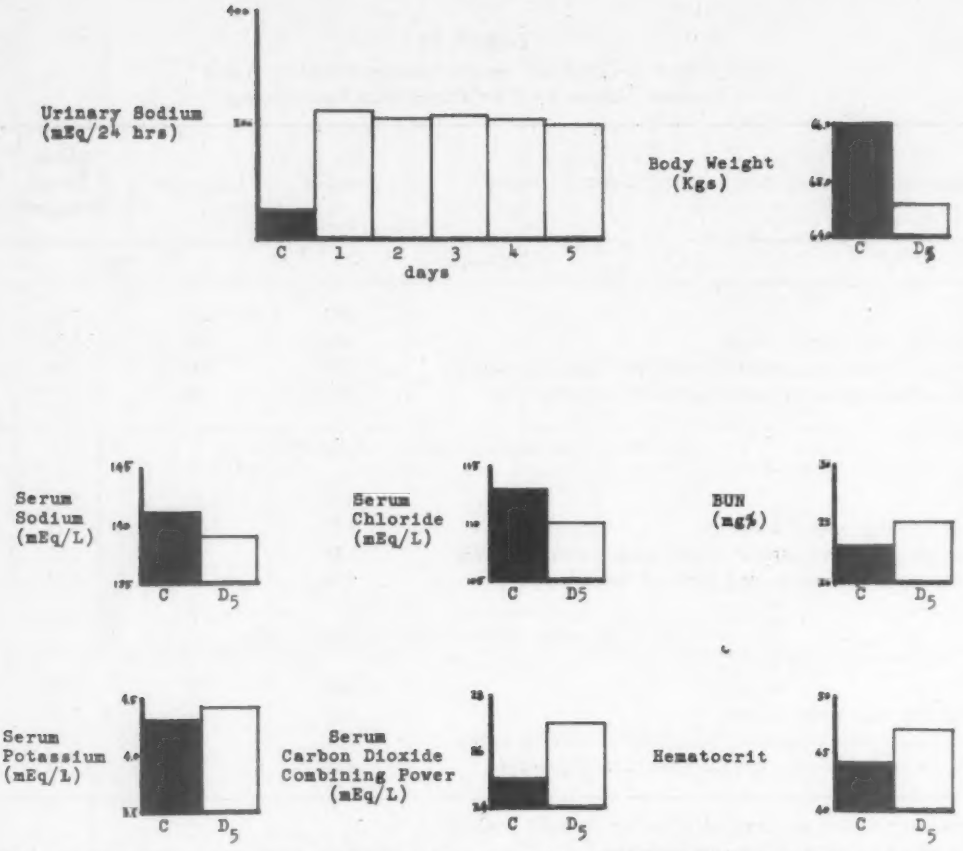

FIG. 6. The effect of continuous therapy (five days) with CMR-807 (8 mg. daily) on urinary sodium and serum electrolytes, blood urea nitrogen and weight (average values for five patients).

and potassium urine excretion data similar to those shown with the five-day excretion data with 8 mg. CMR-807. The sodium increase continued until all excessive body stores of sodium had been depleted. The potassium excretion increased minimally for the first two days and then returned to control levels. Serum electrolyte levels showed no significant changes during the twenty-one–day period.

COMMENTS

CMR-807 (Naqua) appears to be a more potent, orally effective, diuretic agent as compared with previously reported thiazide diuretics. Concomitant with this increased potency as a natriuretic agent, CMR-807 has somewhat different effects on electrolyte excretion than either chlorothiazide or hydrochlorothiazide. With this diuretic there is primarily a lessening of potassium and bicarbonate excretion and pH change which may be significant in decreasing the incidence of such hypokalemic manifestations as subjective weakness and electrocardiographic changes.

CMR-807 is effective on repetitive daily use and is not associated with significant serum electrolyte changes. At no time were indications of toxicity or clinical reversal observed, even with double the maximum effective dose of 8 mg. The drug is effective in many edematous states (Table III), regardless of the etiology of the edema. As an adjunct in the management of hypertension, it is of distinct value and can effectively replace presently used diuretics such as chlorothiazide (Table II).

SUMMARY

A new benzothiadiazine derivative, Naqua (CMR-807), is a more potent, orally effective diuretic than similar diuretic agents reported to date. It produces less potassium and bicarbonate loss with a lessened tendency toward hypokalemic manifestations. It is repetitively effective, has no toxicity in the doses used in this study and represents a distinct advantage in the control of the manifestations of hypertension and edematous states of varied etiology.

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The Use of Hydroxyzine in the Prophylaxis and Therapy of Cardiac Arrhythmias

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REPORTS continually appear in medical literature concerning the use of new, safe, broad spectrum antiarrhythmic drugs. The chief factors responsible for efforts directed in this regard are twofold: (1) the profound side effects attributable to the agents now in general use and (2) the need for a drug which will have a broad scope of action not only in the therapy of arrhythmias but also in the prophylaxis of arrhythmias.

Recently, animal studies[1] and clinical trials[2] in man utilizing the drug hydroxyzine have been encouraging. Reportedly this agent was found to be safe, non-toxic, easily administered, and clinically effective in converting to sinus rhythm twenty-six of thirty-four cases of ventricular extrasystoles, auricular extrasystoles, paroxysmal atrial tachycardias, and paroxysmal ventricular tachycardias. The success in converting atrial fibrillation was limited to four of the sixteen cases. Dosages used varied between 25 to 75 mg. administered intravenously, 50 to 100 mg. given intramuscularly and 10 to 25 mg. given orally, four times a day.

Our present study deals with the response to the parenteral administration of hydroxyzine of patients with various arrhythmias, the majority undergoing constant electrocardiographic monitoring.

MATERIAL AND METHOD

Hydroxyzine was administered parenterally to ten patients presenting at our office with acute or chronic arrhythmias and these were monitored by continuous electrocardiograms. In addition, this drug was administered orally to three hospitalized patients, one immediately following an acute myocardial infarction, one following a simple mastectomy and one suffering from digitalis toxicity. None of these was given other cardiac drugs simultaneously.

RESULTS

In ten of these thirteen patients, no appreciable beneficial effect was noticed. One patient reverted to sinus rhythm while receiving the medication and in one a severe arrhythmia developed while under therapy. One patient showed fewer extrasystoles, but these were not abolished completely. The results are summarized in Table I.

COMMENT

Hydroxyzine was originally introduced as one of the "tranquilizing" drugs. It is chemically related to the antihistamine group because of its basic benzhydryl and piperazine configuration. Ende[3] reported its favorable effect in allaying anxiety and tension in seventy-six of one hundred subjects given a dosage ranging from 10 to 50 mg. three times a day. This included improvement in seventeen to twenty-four patients with anxiety associated with cardiac disease, cerebral arteriosclerosis, diabetes and other disease states. No side effects were noted. Burrell and his colleagues[2] believed that its antiarrhythmic action, although admittedly unknown, was not a tranquilizing or sedative effect via the central nervous system.

In our study the only patients showing a favorable response were a sixty-five year old woman with nodal tachycardia (Fig. 4) and an eighty-five year old woman with frequent auricular extrasystoles. It is our belief that the ataractic effect achieved with hydroxyzine was chiefly responsible in these cases for the effect in the rhythm. While the calming ability is certainly desirable in a patient with paroxysmal tachycardia or other arrhythmia, the specific antiarrhythmic effect anticipated was not achieved in the majority of cases.

No side effects were noted by Ende and Burrell in their studies with the exception of drowsiness. In one of our subjects an undesirable side effect

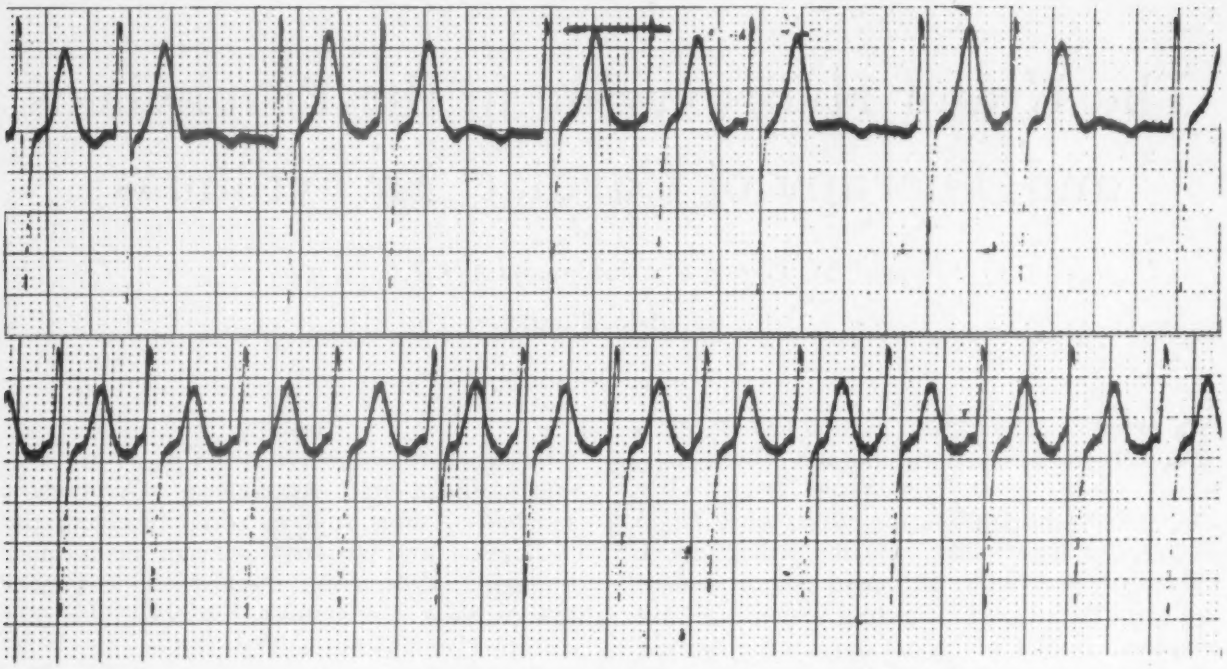

FIG. 1. Case 2. *Top*, control tracing, lead V_3, showing atrial tachycardia with varying A-V block. *Bottom*, five minutes after the intravenous administration of 25 mg. hydroxyzine. Tachycardia has become regular with 2:1 A-V response due to atropine-like effect.

TABLE I

Case No.	Rhythm	Dosage and Route of Administration	Result	Remarks
1	Atrial fibrillation	25 mg. 3 times a day, orally	No effect	Possibly due to digitalis toxicity
2	Atrial tachycardia	25 mg. intravenously 50 mg. intramuscularly	No effect	45 minutes after intravenous dosage. See Figure 1
3	Ventricular premature contractions	75 mg. intravenously	No effect	...
4	Paroxysmal atrial tachycardia	25 mg. intravenously	No effect	Has Wolff-Parkinson-White Syndrome. See Figure 2
5	Paroxysmal atrial tachycardia	75 mg. intravenously	No effect	See Figure 3
6	Paroxysmal A-V nodal tachycardia	75 mg. intramuscularly	Reversion to sinus rhythm	See Figure 4
7	Ventricular premature contractions	100 mg. intramuscularly	No effect	...
8	Paroxysmal atrial tachycardia	25 mg. intravenously	No effect	...
9	Chronic atrial fibrillation	50 mg. intravenously	No effect	...
10	Sinus rhythm	25 mg. 4 times a day, orally	Developed atrial fibrillation	Acute myocardial infarction
11	Atrial premature contractions with bigeminy	10 mg. 4 times a day	Decreased frequency of APC's	With simple mastectomy
12	Ventricular premature contractions	50 mg. intravenously	No effect	...
13	Paroxysmal A-V nodal tachycardia	50 mg. intravenously 50 mg. intramuscularly	No effect	...

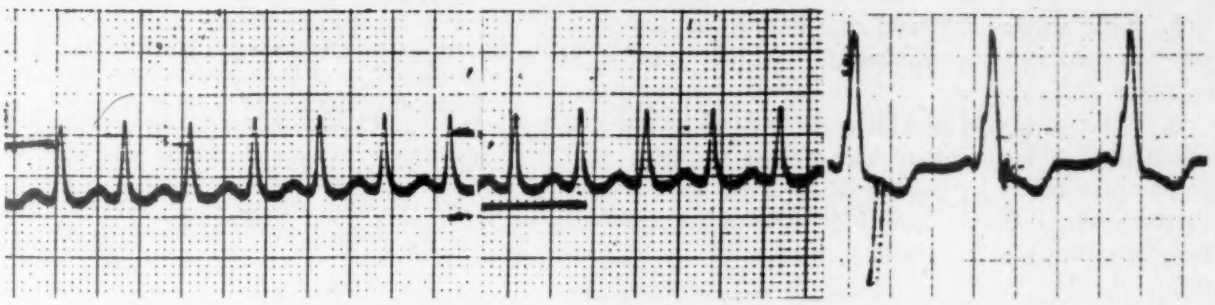

FIG. 2. Case 4. *Left*, control tracing, lead I, showing paroxysmal atrial tachycardia. *Middle*, ten minutes after the intravenous administration of 25 mg. hydroxyzine, no effect on tachycardia. *Right*, thirty-five minutes after the intramuscular administration of 0.2 gm. quinidine, normal sinus rhythm with WPW syndrome.

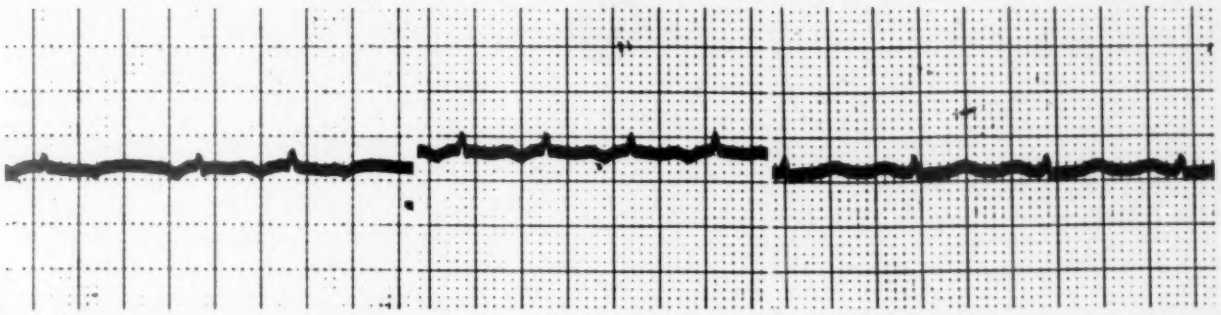

FIG. 3. Case 5. *Left*, control tracing, lead aVF, showing atrial tachycardia with varying 1:1 and 2:1 A-V conduction. *Middle*, forty minutes after the intravenous administration of 75 mg. hydroxyzine, showing 1:1 A-V response due to atropine-like effect of the drug. *Right*, conversion to sinus rhythm five minutes after the intravenous administration of 0.6 mg. Cedilanid.

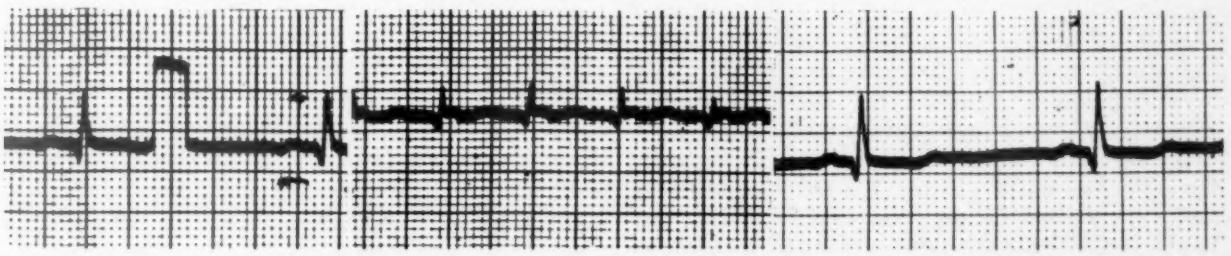

FIG. 4. Case 6. *Left*, control tracing, lead aVL, showing normal sinus rhythm. *Middle*, development of paroxysmal nodal tachycardia while tracing was recorded. *Right*, conversion to normal rhythm thirteen minutes after the intramuscular administration of 75 mg. hydroxyzine.

was observed consisting of flushing, dyspnea, and palpitation unaccompanied by changes in rhythm or blood pressure. Indeed, this patient later recalled suffering extreme nervousness and malaise when given the drug orally by another physician previously.

In addition, a specific action of hydroxyzine, its atropine-like effect, proved undesirable in two subjects with atrial tachycardia. Here the degree of atrioventricular block was lessened and the ventricular rate increased.

CONCLUSION

1. Hydroxyzine was administered to twelve patients with cardiac arrhythmias including atrial fibrillation, paroxysmal atrial tachycardia, ventricular premature contractions, paroxysmal nodal tachycardia and atrial premature contrac tions. One subject with sinus rhythm received the medication prophylactically.

2. In one case of nodal tachycardia, conversion to sinus rhythm was achieved and in one case the frequency of auricular extrasystoles was reduced.

3. All other subjects were refractory to hydroxyzine.

4. In the patient with acute myocardial infarction given hydroxyzine prophylactically atrial fibrillation developed while receiving the drug.

5. One subject suffered side effects consisting of palpitation, flushing, dyspnea and anxiety.

6. The atropine-like effect of hydroxyzine resulted in a lessening of the degree of atrioventricular block in two cases of atrial tachycardia (Figs. 1, 2 and 3). This was considered to be an undesirable action.

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Maintenance Quinidine Therapy*

Value of Enteric-Coated Quinidine Tablets

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MOST ectopic tachycardias can be terminated with quinidine therapy. Subsequent maintenance of sinus rhythm for prolonged periods may prove difficult, however. Recurrence of the arrhythmia may be associated with selection of an inadequate maintenance dose, but more often results from sporadic omission of the drug because of the requirement for frequent doses. Failure of maintenance therapy has also been attributed[1,2] to the low blood levels to be expected at 7 or 8 A.M. when the last evening medication is given at 9 or 10 P.M.

The use of an enteric-coated quinidine preparation might be expected to prolong effective serum levels of the drug and reduce the frequency of doses necessary for successful maintenance of quinidine therapy. Previous studies[1-3] have, in fact, shown adequate plasma quinidine concentration twelve hours after the oral administration of enteric-coated quinidine tablets. Serum levels following a delayed absorption form of quinidine have not been compared previously with concentrations obtained after the administration of ordinary quinidine to the same subject in similar dosage. The current investigation reports serum quinidine concentrations in seventeen subjects, each of whom received both U.S.P. quinidine and a delayed absorption quinidine compound.† The effect of single dosage and of multiple-dose schedules of each preparation on serum levels was observed.

† Quinidine Extentabs® supplied through the courtesy of A. H. Robins Co., Richmond, Virginia.

METHODS

Subjects were hospitalized patients with various cardiac arrhythmias. Although cardiomegaly was demonstrated in most of the patients, congestive failure or azotemia was not present in any patient at the time of the study.

Single doses of each preparation were administered at 9:00 A.M. In multiple dosage schedules, regular quinidine was given at 9 A.M., and at 1, 5 and 8 P.M., while the delayed absorption preparation was given at 9 A.M. and 9 P.M. Meals were eaten at usual times.

Serum quinidine levels were measured fluorimetrically using the precipitation method of Brodie and Udenfriend[4] and an Aminco photofluorimeter. Quadruplicate determinations of the same sample agreed within plus or minus 4 per cent for concentrations greater than 1 mg./L. Concentrations are reported as milligrams of quinidine sulfate per liter of serum. (Quinidine base comprises 83 per cent of quinidine sulfate.)

RESULTS

CHANGES IN SERUM QUINIDINE CONCENTRATION

Single Doses: Measurements of serum quinidine concentration were made just before and at 2, 4, 6, 8, 12 and twenty-four-hour intervals after the administration of a single dose of 0.8 gm. quinidine sulfate U.S.P. to seven subjects. Similar observations were made following the administration of 0.9 gm. quinidine Extentabs in the same seven subjects. Figure 1 shows the average and extreme serum levels observed following each medication.

Following the administration of 0.8 gm. U.S.P.

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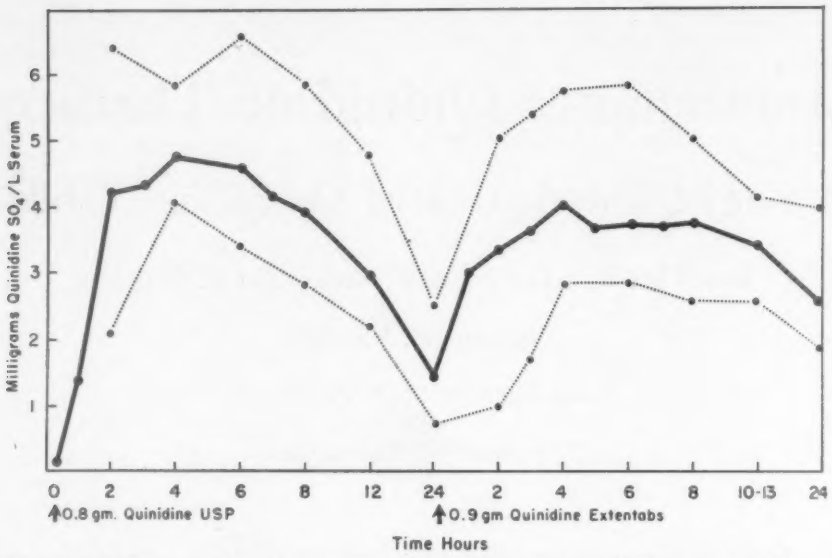

FIG. 1. Serum quinidine concentrations observed after single doses of U.S.P. quinidine sulfate, and an enteric-coated sulfate preparation (Extentabs). The solid line denotes the average of individual values in seven subjects, and dotted lines the highest and lowest individual values.

quinidine, maximum serum concentrations occurred in two to four hours and continued to eight hours, with decrease to about two-thirds of peak levels at twelve hours and a fall to one-third peak level at twenty-four hours.

After the administration of 0.9 gm. of the delayed absorption preparation (Extentabs), maximum serum levels were obtained in the two- to eight-hour period, and averaged about 15 per cent lower than those with U.S.P. quinidine. At twelve hours serum quinidine concentration was 17 per cent higher, and at twenty-four hours, 66 per cent higher after the administration of Extentabs than after the administration of U.S.P. quinidine.

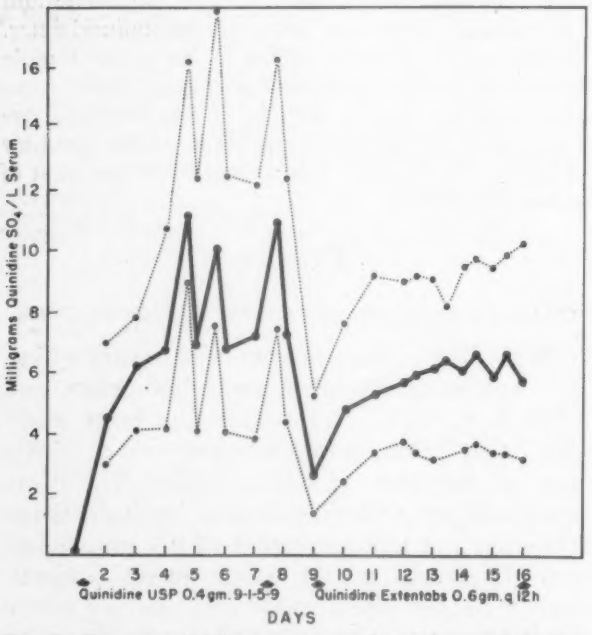
Milligrams Quinidine SO_4/L Serum
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Quinidine USP 0.4 gm. 9-1-5-9
Quinidine Extentabs 0.6 gm. q 12h
DAYS

FIG. 2. Serum quinidine concentrations observed during continual administration of U.S.P. quinidine sulfate, 0.4 gm. four times daily, and quinidine Extentabs, 0.6 gm. twice daily. The solid line connects the average of individual values in ten subjects. Dotted lines denote the highest and lowest individual values.

Multiple Dose Schedules: To each of ten subjects, 0.4 gm. U.S.P. quinidine was administered at 9 A.M., 1, 5 and 8 P.M. daily for eight days. Serum quinidine concentration was measured fifteen minutes before the 9 A.M. dose every day, and ninety minutes after the 8 P.M. dose on the fourth, fifth and seventh days. Beginning thirty-six hours after the last dose of ordinary quinidine, each subject received 0.6 gm. quinidine Extentabs twice daily, at 9 A.M. and 9 P.M. for seven days. The lower dose of Extentabs was chosen since the number of pills (two twice a day) seemed optimum for patient acceptability in long term therapy. Serum quinidine levels were measured daily before the morning dose, and five hours after the morning dose on the fourth, fifth and seventh days of treatment with the delayed absorption preparation.

Figure 2 demonstrates changes in serum quinidine concentration obtained with both preparations. After three days of therapy with U.S.P. quinidine, morning serum levels, drawn twelve hours after the last preceding dose, averaged 7 mg./L., and stayed at this level during the subsequent five days of the study.

Blood drawn one and one-half hours after the last evening dose contained quinidine in concentrations averaging 10 to 12 mg./L. Serum concentrations as high as 18 mg./L. and as low as 4 mg./L. were observed on this schedule. Thirty-six hours after the last dose of medication, detectable quinidine concentrations were still present, averaging 2.5 mg./L.

After three days of quinidine Extentab administration, morning serum quinidine concentration averaged 5 mg./L. and afternoon levels 6 to 7 mg./L. The serum concentrations ranged from low values of 3 to high values of 10 mg./L. (Fig. 2).

As indicated by the wide range of quinidine concentrations (Figs. 1 and 2) there was considerable individual variation in the serum level produced by both types of quinidine. In general, subjects in whom high concentrations were produced by U.S.P. quinidine also had high concentrations while taking Extentabs. Low serum concentrations also occurred with both forms of the drug in individual subjects.

CLINICAL CORRELATES

Nausea and tinnitus were noted in two patients receiving 0.4 gm. U.S.P. quinidine four times daily. No symptoms were associated with the administration of the delayed absorption preparation. One patient, receiving 0.4 gm. U.S.P. quinidine four times daily for the sixth day, had a sudden change in heart rhythm from atrial fibrillation to atrial tachycardia without heart block. His ventricular rate rose to 180 and his blood pressure fell to 50/30 mm. Hg. Serum quinidine concentration was 6 mg./L. No other serious complications of quinidine therapy occurred in these seventeen patients.

COMMENTS

The most striking difference between the two forms of quinidine lay in the marked elevations of serum quinidine concentration occurring at night in patients receiving U.S.P. quinidine in doses commonly used for maintenance therapy. After four days of plain quinidine, 0.4 gm. four times daily, blood drawn one and one half hours after the nighttime dose contained an average of 11 mg. quinidine sulfate per liter of serum, with the lowest such nighttime level being 8 mg./L. and the highest 18 mg./L. If the ten patients studied are representative of the total population receiving maintenance quinidine in these doses, it is surprising, in light of the high nocturnal quinidine concentrations, that toxicity is not more frequent.

The data reported prove false the hypothesis under which this study was initiated, namely, that early in the morning blood quinidine concentrations might fall to such low levels as to permit recurrence of arrythmia in patients receiving U.S.P. quinidine. Morning levels, eleven to twelve hours after the last previous dose, averaged 6 mg./L. after the third day in patients receiving 0.4 gm. quinidine U.S.P. four times daily. The lowest level observed after the second day on such a schedule was 4 mg./L.

Administration of quinidine Extentabs was associated with much less fluctuation in serum quinidine concentration. Values obtained four hours after a dose of the long-acting preparation were insignificantly different from values twelve hours after the last dose. Although the experimental design prevents direct comparison of blood levels produced by identical maintenance doses of the two drug forms, it is probable that serum concentrations existing throughout the day in patients receiving Extentabs twice daily will be similar to early morning concentrations observed in patients receiving equal doses of U.S.P. quinidine administered four times a day.

Administration of U.S.P. quinidine in maintenance doses of 0.4 gm. four times daily produced morning serum quinidine concentrations which were constant from the fourth day through the eighth day. This finding contrasts with that of Sokolow and Edgar[5] who found that the morning serum quinidine concentration was lower each day after the fourth day than on the preceding day in each of four subjects. No explanation can be given for this difference in the effect of constant daily dosage on serum concentration between Sokolow's patients and the present group, and, in fact, Sokolow states "further experience with fixed daily doses of quinidine has shown that in some cases the daily maximum blood level falls only slightly or not at all after the peak levels have reached a plateau in two to five days." Our data suggest that serum quinidine concentration remains constant from day to day, at any given time of day, once the third day of constant dosage has been passed.

Serum quinidine levels obtained with single doses of 0.9 gm. of the delayed absorption quinidine sulfate preparation used in this study were quite similar to those obtained by Bellet[2] using a single dose of 1 gm. enteric-coated

quinidine gluconate in ten normal subjects. Our values are slightly higher than concentrations observed by Sampson et al.[3] in seven patients after administration of 0.8 gm. of enteric-coated quinidine sulfate. In Sampson's patients, peak levels occurred five to twelve hours after the administration of quinidine, and ranged from 2.3 to 3.3 mg./L., whereas, with the preparation used in the current study, maximum levels of about 4 mg./L. occurred in the two to eight-hour period.

Summary

Serum quinidine concentrations were measured after the administration of both U.S.P. quinidine sulfate and a delayed absorption quinidine sulfate preparation (Extentabs) to each of seven subjects in single doses of 0.8 gm. and to each of ten subjects in maintenance doses for an eight-day period.

Following single doses, blood levels were slightly lower and slightly more prolonged with the delayed absorption form than with the U.S.P. compound. The administration of U.S.P. quinidine, 0.4 gm., at 9 A.M. and 1, 5, and 8 P.M. daily, produced high morning blood levels (average 7 mg./L.) after the third day, and very high nighttime levels (average 11 mg./L.). Quinidine Extentabs, given to the same subjects but in a slightly lower dose of 0.6 gm. twice daily, produced average serum concentrations of 6 to 7 mg./L. which remained relatively constant throughout the day from the third to eighth day.

Maintenance therapy with U.S.P. quinidine, as commonly administered, is not accompanied by low serum concentrations early in the morning. The long-acting preparation used in this study produced adequate serum concentrations with a dosage schedule more convenient than the schedules required by U.S.P. quinidine.

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Historical Milestones

Emotions and Angina Pectoris

An Historical Review*

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Boston, Massachusetts

THE SYMPTOMATOLOGY, course and termination of the syndrome "angina pectoris," first presented in the description of Heberden[1] in 1768, has been elaborated by countless observers since that time. The practicing physician, who has to treat people afflicted with this disease, probably has felt inadequate when the conventional technics of therapy have failed to halt or modify the sudden and fatal outcome; and particularly so in those cases when the patient was comparatively young and healthy, the pain slight and occasional, and the prognosis optimistic. The occurrence of sudden death could completely shatter a hitherto complacent clinical management. The fact that many of the attacks occur in relation to specific persons and situations has led to the realization that the patient's attitudes and associated emotional states also are important determinants of the disease state and that the variations in his reactions to situation and person may decide whether or not an attack will occur.

The influence of emotions as a precipitating factor and as a cause of death in this disease had been known to Heberden and to a host of clinicians who followed him. Lacking the precise technics of diagnosis which we possess today they devoted considerable time and attention to the attempt to identify, define and control the associated emotional states.

The historic contributions of the past few centuries dealing with the etiology, prophylaxis and treatment of angina pectoris have been arranged into three general categories. Overlapping has been unavoidable because of the nature of the material.

THE ROLE OF SOCIAL AND CULTURAL INFLUENCES AND EMOTIONS IN GENERAL

Corvisart,[2] in the introduction to his treatise on heart disease, presents his Ideal Physician.

> "In truth, to what errors does that Physician expose himself in his professional career, who neglects the important study of moral man? The slightest attention to the social state, particularly in large cities, where all the passions, and the vices in all their shades, and under all their possible forms, animate, excite, and put into motion the whole system, above all the nervous, in a thousand various and opposite ways, affords striking and daily proof of this assertion: and if we reflect, moreover, on the disturbance thus produced in the viscera throughout the whole economy, we shall find all the functions, more or less, disordered by these ever-agitating or ever-renewing causes: we shall behold the inadvertent Physician losing himself in the choice of his means, and almost always deceived in the results which he promised himself."

Speculations about the etiology of organic heart disease were closely connected with the prevailing social conditions. Selected for emphasis were the passions aroused, the goals and the general social state of the individual.

Corvisart, working as a physician and cardiologist during the time of the French Revolution and the "Reign of the Terror," was profoundly impressed by the increase in heart disease. This increase, which caught and held his attention more than any other, was considered to be the effect of the emotions. His discussion opens:

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"Let me speak of the influence of moral causes, and especially let me name the passions. Shall I venture to say, that, by a deplorable fatality, the noblest passions, the sublimest feelings, react also on the heart, and often derange its action."

And further on he asked that if "anyone can seriously deny, or even doubt the fatal physical influence of the passions upon the heart, it surely will be sufficient for him to know that it sometimes bursts in a fit of passion, and causes instant death." Quite emphatically he proclaims: "I am not the only physician who has thought, that Organic Lesions of the heart were more frequent, during the horrible periods of the revolution, than in the usual calm of social order. The calamitous events, the bloody scenes of the revolution, the loss of property, the arrests, the emotions and grief occasioned by them, have furnished in our time ample proof of the influence of the passions in exciting organic diseases in general, and those of the heart in particular. How many persons once opulent, but then reduced to beggary, have been seen in hospitals praying for speedy death, as a termination to their miseries, in whom an organic disease of the heart was drawing on too slowly for their wishes?"

The physicians of the nineteenth century did not concern themselves with speculations regarding the general etiology of heart disease. The introduction of the stethoscope by Laennec had opened a new dimension in the diagnosis of heart diseases. Those fascinating sounds and murmurs caught the imagination, and directed the investigative energies of the century, just as the electrocardiograph and the x-ray did in the next. As the century continued, the textbooks on cardiology became thicker and the periodical literature more abundant. Physical diagnosis dominated the period. However, here and there an occasional voice was heard giving forth a thought on social or emotional causation of heart disease. Such a voice belonged to Wooster[3] who practiced cardiology in San Francisco during the period of the gold rush and has left us in the introduction to his book on heart disease some reflections on etiology. He states:

"Cases of heart disease are of alarming frequency in California, yet, in the absence of statistics, it would be improper to say categorically that this affection is excessively frequent here; still I feel convinced that it is, and were its etiology within the scope of this treatise, I think it could be satisfactorily shown why disease of the heart is more likely to be prevalent in newer than in older civilisations, and in this climate than in many others; and under the special, moral, mental, and hygienic influences which characterize us, than under those which predominate in other centers of population."

Another powerful and polished voice was that of Osler,[4] the outstanding clinician of his day. Writing on arteriosclerosis in general, and angina pectoris in particular, he observed:

"In the worry and strain of modern life, arterial degeneration is not only very common, but develops often at a relatively early age. For this I believe that the high pressure at which men live, and the habit of working the machine to its maximum capacity, are responsible, rather than the excesses in eating or drinking, or than any special prevalence of syphilis, Angeiosclerosis, creeping on slowly but surely, 'With no pace perceived,' is the Nemesis through which Nature exacts retributive justice for the transgressions of her laws—coming to one as an apoplexy, to another as an early Bright's disease, to the third as an aneurysm, and to the fourth as angina pectoris, too often slitting the 'thin spun life' in the fifth decade, at the very time when success seems assured. Nowhere do we see such an element of tragic sadness as in many of these cases."

Social and Occupational Influences: During the eighteenth and nineteenth centuries it was noted that the disease did not affect all sections of the population but seemed to restrict itself to certain social classes. There was considerable agreement that the disease was rare in general hospitals as late as 1910;[9,19] that the victims were usually males over the age of fifty, many of whom were men of great intellectual attainment;[10] that they belonged to the more highly educated and refined classes;[11] that it was rare in laborers and farmers but very frequent among those in liberal professions: doctors, lawyers priests, politicians, financiers and industrial magnates.[12–14]

A striking confirmation of these observations has recently been published by Ryle and Russell.[5] It was demonstrated that if the population was divided into five social classes, class I being largely composed of professional workers, class III of skilled artisans and class V of unskilled workers, the remaining two classes being intermediate, the standard mortality ratio (S.M.R.) was almost three times greater for class I than class III, and almost four times greater than class V. The sex ratios showed a similar interesting relationship. For class I the male death rate in the age period of forty-five to fifty-five was almost ten times that of the female death rate, whereas in the lowest social class (class V) it was three times greater. Of even greater interest to the medical

profession is that physicians and surgeons headed the list with the highest mortality, with a standard mortality ratio of 368; proprietors of wholesale business came next with 235; the legal profession, third, with 227; and clergymen, fourth, with 218. At the other end of the list, workers in chemical processes had the lowest with a standard mortality ratio of 20; agricultural laborers, 32; stone miners and quarriers, 38; and coal miners, 40.

The Role of Specific Emotional States, Notably Anger

Heberden, in his description of the disease, remarked about the effect passions of the mind had on the disease. Before the eighteenth century had come to a close the specific effect of anger, both as a precipitating cause of the paroxysms and as a cause of death, had been established. For example, Fothergill[6] describes the case of a sixty-three year old male patient, who on the evening of March 13, 1775, in a sudden and violent transport of anger, fell down and died immediately. But it was through the life and death of one of the most remarkable physicians of the age, Hunter,[7] that the effects of the emotions were so emphasized and dramatized.

"It is a curious circumstance that the first attack of these complaints was produced by an affection of the mind, and every future return of any consequence arose from the same cause and although bodily exercise or distension of the stomach brought on slighter affections, it still required the mind to be affected to render them severe, and as his mind was irritated by trifles, these produced the most violent effects of the disease. Most of the attacks of angina pectoris described were brought on by 'anxiety or anger.'

Indeed, he was accustomed to say 'that his life was in the hands of any rascal who chose to annoy and tease him.' As he had himself predicted, death came suddenly, in consequence of a fit of temper at a meeting of the governors of St. George's Hospital, October 16, 1793. The coronary arteries were found to be converted into open bony tubes, and the aorta was dilated."[9]

The effect of anger on angina pectoris began to receive additional confirmation as more and more physicians became acquainted with the disease. As their experience with it as a pathologic and clinical entity increased, many began to regard anger as the most important force to be manipulated in therapy and prophylaxis.

As early as 1781, Fothergill, in the same work previously quoted,[6] advises one on prophylaxis, "to guard against passion or any vehement emotions," and feels that "it is not improbable, but if on the first appearance of this stricture (anginal pain) one might greatly retard the progress of this disorder by assisting to restrain excess of passion and anxiety, which perhaps, contribute more to the increase of this disease than a combination of all the other causes."

Desportes[8] in a similar vein, while discussing predisposing causes of the disease, remarks that the symptoms are "most certainly brought on by disturbance (emotional) as joy, sadness, and above all by bursts of anger, even though the body is at rest" and that "sudden death has often been the result of the attacks induced by emotional cause."

Forbes,[15] in his comprehensive article on angina pectoris, wrote in 1845 that "a most important chapter in the history of all diseases immediately connected with the functions of the heart, is that which treats of their relation to mental impressions; and in no case is the consideration of this relation so important as in the prophylaxis of angina. But no one who has lived in the bustle of life, and seen much practice, will doubt for a moment that the mental states now referred to are among the most prevalent and most influential of the remote causes of such diseases. When angina already exists, it must be admitted that these, as well as the exciting passions, are among the most frequent exciting causes of the paroxysm. Very many examples of sudden death from anger, in diseases of the heart, are recorded; and not a few of these have occurred in the cases of angina. These statements prove the great importance of mental discipline in this disease; and although 'herein the patient must minister to himself,' it is the duty of the physician to point out to him the necessity no less of the moral than the physical means of prophylaxis."

Latham[16] remarked that a man may resolve never to move from his chair, "but he cannot resolve never to be angry." Thus many a person with angina pectoris, who by skillfully measuring and limiting the movements of his body by what he can bear, has been able to abate the frequency and severity of the paroxysms and so prolong his life for years, has, in an unhappy moment, been surprised into anger and died at once. . . . "And so I believe then in angina pectoris, death has followed mental excitement more frequently than bodily excitement."

Wardrop,[17] a consultant cardiologist to William IV in his last illness, had a great deal to say about the effects of the passions of the mind on congestive failure and angina pectoris. In his treatise on "Diseases of the Heart," after discussing sudden death as a result of emotional trauma in apparently normal people he continues with the observation:

"The effects of the passions of the heart are still more remarkable when the heart is previously in a diseased condition; and so great is this influence that

there are many instances of persons afflicted with a diseased heart who have perished suddenly from some violent emotion." John Hunter is mentioned as a celebrated example; also the case of the well known actor, Palmer, who, while performing the part of the "Stranger," became so impassioned that immediately after reciting "There is another and a better world," he dropped, lifeless. Wardrop continues, "Indeed, on reviewing cases of affections of the heart which have come within my observation, it is remarkable in how many instances they could be distinctly traced to some sudden or violent mental excitement." He is convinced that certain diseases of the heart that produce congestive failure, those associated with coronary artery disease and myocardial dilatation, owe their origin to a moral cause for "this powerful influence of the mind ought surely be an useful lesson to medical men in the moral treatment of those with a disorder of the heart."

Trousseau,[18] a prominent French teacher and clinician of the nineteenth century wrote in his justly popular textbook on medicine that in angina pectoris "deep mental emotions especially anger are frequent exciting causes—bring on paroxysms, and may increase the intensity of the disease to such a degree as to bring on death."

Hall[10] believed that it is of "supreme importance to direct attention to the mental condition of the patient," for he had seen "one case in which the first and only attack of angina pectoris followed by death in two or three days, was brought on by a violent altercation of the patient with his son, and that these and numerous other cases should lead us to enjoin upon our patients the necessity of cultivating an equable temper, and nipping in the bud any tendency to an outburst of anger, however just."

Osler's Views on Emotions, Mode of Life and Angina Pectoris: Osler,[19] in his Lumleian Lectures published in 1910 written more than a decade after his book on angina pectoris, speaks to his medical audience in a vein reminiscent of an intimate talk of one experienced physician to another. Here he is concerned with the life situations, emotional reactions and social station of his patients. He, like others before and after him, noted the frequency with which physicians are victims of the disease. The observations most pertinent to the theme of his paper are given in the following extracts.

Racial Incidence: Thirty-seven were Jews "living an intense life, absorbed in his work, devoted to his home, the nervous energy of the Jew is taxed to the uttermost and his system subjected to that stress and strain which seems a basic factor for so many cases of angina pectoris."

Angina in Doctors: "A point that stands out prominently in my experience is the frequency of the disease in our profession. Angina may almost be called 'morbus medicorum,' thirty-three cases were physicians, a larger number than all the other professions put together. Curtain in his study of fatal cases noted that one-fourth were physicians. The frequency with which doctors die from the disease has become the subject of common remark. From John Hunter onward a long list of distinguished men have been its victims . . . among our contemporaries was Nothnagel, one of the ablest students of the disease, whose last act in life was to describe his own fatal attack. Charcot, the founder of the modern neurology died from it in Paris last winter. The most brilliant and devoted physician of his generation in the United States, the late William Pepper, died of coronary arteries like pipe stems at fifty-five. In a group of twenty physicians every one of whom I know personally the outstanding feature was the incessant treadmill of practice and yet if hard work alone was responsible would there not be a great many more cases. Every one of these men had an added factor—worry."

Comments on the Circumstances Connected with the Onset of the Attacks: "A man of great mental and bodily energy working early and late in practice, involved in speculations in land; domestic infelicities; worries in the Faculty of Medicine; troubles with the trustees of his institution; law-suits, domestic worries, and so through the list."

Comments on Emotional Relationships: Osler believed that emotion was the most common but least serious cause of angina pectoris. For example, he presents the case of a physician, a well known author, who would experience an attack of angina while lecturing and at no other time. Another physician "could lecture and hold his clinic without experiencing any difficulty, but if he read a paper before the Medical Society or if he gave an address in public, the substernal tension was certain to come on." As an example of death following a public appearance, Osler cites the case of Mr. G., age thirty-nine, an extraordinarily vigorous, muscular man, who, after a full day of effort and strain, read an important paper at a college society and died the following night during an attack. He also was aware of the fact that in some fatal cases no lesions of the coronary vessels, the pericardium or the cardiac nerves were demonstrated.

Character Descriptions: "It is not the delicate neurotic person who is prone to angina but the robust, the vigorous in mind and body, and the keen and ambitious man, the indicator of whose engines is always at 'full speed ahead.' There is indeed a frame and facies at once suggestive of angina—the 'well set man of from forty-five to fifty-five years of age, with military bearing, iron grey hair, and florid complexion.' "

Prognosis: Much depends on the patient himself—on the life he has led—the life he is willing to lead. The ordinary high pressure business or professional man may find relief or even cure in the simple process of slowing down the engines. The difficulty is to

induce a man of this type to lessen "the race, an' rack, an' strain." As William Pepper used to say ("Pepper, the provost, indeed the maker of the great University, the very head and front of every important public movement in a city of a million inhabitants, a universally sought consultant and enthusiastic teacher, a prolific author, in him was incarnate the restless American spirit which drove him into a premature grave at the height of his career at the comparatively early age of fifty-five"), "Give me the life of a hare rather than the existence of a tortoise." Not even the terrible outbursts of pain may suffice to check men of this stamp. We doctors are notorious sinners in this respect, but it is so hard to lessen work when in full swing . . . and how few of us at fifty or fifty-five years of age are able to do this. A severe attack of angina may save the life of a man. Many instances of slight anginal attacks are brought on by anger, worry or sudden shock. Yet the cause is rather easy to avoid.[11] (Although John Hunter and many others neither thought nor found it so.)

Although, of the emotions emphasized, anger was by far the most prominent, extreme joy, triumph or elation did not escape the vigilance of these clinicians. Desportes, Balfour, Wardrop, Huchard and others had noted the effects of these elated states on the course of the disease and recorded examples of sudden death produced by them.

The Role of Neurosis

Starting with the historic discovery of Jenner of the association of "ossification" of the coronary arteries with angina pectoris (which was sent as a personal communication to Parry,[20] who included it in his famous work "Syncope Anginosa"), the "coronarian hypothesis" as it was called, slowly became established as the explanation for the various pathologic and clinical manifestations. It was not received without dispute, however, for a rival hypothesis was presented by the French clinicians and pathologists, namely that of an inflammatory process of the vagus and phrenic nerves and the cardiac plexus.[23,24] These contentions arose from the attempt to explain the paroxysmal character of the symptoms, the influence of the emotions and the lack of correlation between the degree of alteration of the coronary vessels and the symptoms.[21,22] Hence the conviction that the disease was a neurosis without coronary alteration or a neurosis engrafted upon the well recognized postmortem finding was held by many of the physicians of the day. Gairdner,[25] in remarking in his exhaustive monograph on the etiology of this disease (1877), concluded:

"Because of the (1) pain suddenly coming and going, (2) the paroxysmal character of the symptoms and absolutely sudden death, on these grounds now as in the time of Heberden, we may assuredly claim for angina pectoris a place among the neuroses acknowledging that neurosis is often present upon organic heart disease also."

Powell,[26] in his lectures on acute cardiac failure, urges that from "a practical as well as scientific point of view, we must regard angina pectoris. . .as a functional disease, a cardiovascular neurosis." And in another paper[27] he quotes Dr. Walshe who maintained that in every case of angina there is some organic change in the heart, aorta or both but "is nevertheless strongly of the opinion that there is neurotic disturbance beyond this change as an essential element in Angina."

Among others, Trousseau[18] regarded the anginal attack as being similar to an epileptic one, and Paul[23] thought it "necessary to compare it with other nervous attacks, epileptic, hysteric, asthmatic, migrainous, etc." Semple[28] believed that angina pectoris was a nervous disease but excluded all cases showing organic disease. It was thought to be caused by some affection of the vagus and phrenic nerve." Williams[11] concluded that in the majority of cases of true angina pectoris "there is the neurotic element" and "the intimate dependence of the attacks on neurotic element was early recognized by Trousseau, and many other clinicians go so far to describe angina as a pure neurosis."

Comments

When a physician describes, for the first time, the discovery of a new disease entity which subsequent experience in the hands of other medical observers proves to be true, the question naturally arises as to the reason for the sudden appearance of the new disease process in a particular place or time in the history of mankind. Is it really new or is it a variant of some other disorder to which it bore such resemblance that newly developed diagnostic technics were required for separation? Or, has diagnostic acumen increased making the recognition inevitable? This question arose in the minds of the earliest observers of angina pectoris. Heberden[1] questioned his older contemporaries who told him that they had seen cases of the disease; but Parry,[20] after a comprehensive review of the medical literature extending from the ancients to his time, stated that "it is somewhat extra-ordinary that so many ages should have elapsed without any notice of its existence, either as a distinct disease, or as a variety of any commonly known," and also that he could find no trace of it in Hippocrates, Aretaeus or in any of those "fathers of medical science so celebrated for

their accurate enumeration of the symptoms." McFarland,[29] in an early essay, expressed astonishment that a disease "so alarming in its symptoms and so direful in its consequences as is angina pectoris could have remained so long unnoticed by physicians." One certainly can wonder how a disease with the dramatic qualities of angina pectoris could have remained unnoticed in both medical and nonmedical literature over the many centuries during which man recorded his observations of himself and the world.

It must not be assumed that an account was not written prior to Heberden, for Gibson[30] in his excellent historical summary of the disease supplies evidence to prove that isolated instances of the disease had been recorded in the seventeenth and early eighteenth centuries. Burckhardt,[31] in his "Civilisation of the Renaissance in Italy," tells of a Franciscan monk, noted as a preacher of prophetic sermons which struck terror into the people, who after one of his own sermons died suddenly of "pain in the chest," in 1513. It can be assumed, but not unequivocally proved, that the disease angina pectoris was probably rare throughout the Western world prior to its appearance in appreciable numbers during the eighteenth century. Most observers would agree that angina pectoris is a modern disease and is as characteristic of our modern world as is the unparalleled achievement gained through the growth of the physical sciences.

Anger, Elation and Angina: The consistent emphasis on anger and elation as being important in provoking the anginal attack and, on occasion, sudden death prompts at least two important questions. First, what connection is there between anger and elation and second, how may they conceivably operate on the heart? Examined casually, the angry and the elated individuals appear to be poles apart. One is frustrated in his wishes and reacts with an intense desire to punish what is regarded as an injustice, the other is gratified in his wishes beyond his expectations and reacts with the physical manifestations appropriate to his new state. Therefore, if anger and elation are regarded as specific patterns of physical activity, their close resemblance becomes apparent immediately. For example, at the conclusion of any athletic contest, where the interest of the supporters of each side is great, the decision is greeted with rage by the losers and joy or exultant rage by the winners. To the disinterested observer the physical activity of shouting and jumping is very much the same in rage and joy. This patterned activity, therefore, is their common bond. Viewed in this light, the anginal episodes arising under such circumstances can be regarded as a form of angina brought on by exertion. Clinically, however, it appears that the partial or complete inhibition of the physical expression of anger or elation is related to the anginal episode. And it must be affirmed that improved self control over the physical expression of rage and elation is characteristic of the socially mature individual.

The nineteenth century clinician had accepted the relationship of coronary atherosclerosis to angina pectoris, but he found it difficult to explain the pain in cases in which there was marked rigidity and calcification of the coronary vessels as being caused by a spasm. This same difficulty exists today. There is little debate that angina pectoris does not exist without coronary heart disease with the exception of cases of severe hemodynamic disturbances (aortic insufficiency, aortic stenosis and patent ductus) or anemia plus severe exertion.[32] Therefore, it seems that to explain the fleeting character of the anginal episode, its considerable daily frequency and the associated coronary atherosclerosis, a mechanism or mechanisms must be adduced that will include them all. An hypothesis based on current experimental, clinical and pathologic data would include the vasoconstrictor effect of the vagus on the coronary vessels, the effect of small intimal hemorrhages secondary to raised intravascular pressure[33] and the anoxiating effect of epinephrine on the myocardium.[34] The brief anginal episodes could be vagal and/or epinephrine-induced and neutralized by nitroglycerin; whereas, non-occluding intimal hemorrhages could explain more prolonged episodes which are relatively unrelieved by nitroglycerin. The effects of anger and elation presumably would activate these mechanisms.

Summary

A review of the relevant historic literature indicates that, from the time of Heberden, "the passions of the mind" were accorded an important place among the predisposing and precipitating causes of angina. The bulk of the clinicians selected rage as the most important emotional state connected with angina pectoris, although the elated state of joy was not neglected.

Furthermore, as the nineteenth century continued, and the characteristic pathologic alterations of the coronary vessels and the heart became widely known and accepted, the conviction arose in the minds of many of the clinicians that, despite the obvious morphologic changes, the clinical pattern of the disease fulfilled their definition of an emotional disturbance that somehow affected the heart; that it was somehow connected with the activities, or as it could be called today, the omnipotent strivings of the professional and upper classes; and that anger was the most dangerous precipitating factor of the symptoms and sudden death.

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Progress Notes in Cardiology

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Benzothiadiazine (Thiazide) Diuretics

WITHIN the past year a variety of new diuretics have become available for the treatment of all forms of edema and hypertension. Those compounds of the benzothiadiazine structure now commercially available are listed in Table I. Structural formulas of these compounds are given in Figure 1. All are potent diuretic agents, producing, in the usual dose range, a marked increase in urinary volume and sodium chloride excretion, and a lesser increase in potassium and bicarbonate excretion. Their electrolyte excretion patterns resemble that of a mercurial diuretic more closely than that of a carbonic anhydrase inhibitor. In contrast to this latter group of diuretics, the benzothiadiazines usually retain their effectiveness on long term therapy.

Diuretic Effect: In all types of edema, including edema produced by cardiac, renal and hepatic disease, drugs such as cortisone, toxemia of pregnancy and premenstrual edema, these "thiazides" are potent, rapid acting and of a very low degree of toxicity. Although they act *in vitro* as carbonic anhydrase inhibitors, their main action in man and animals seems to be due to decreased renal tubular reabsorption by a mechanism or at a location different from that of the mercurials. Studies of renal function show no significant change in glomerular filtration rate or renal plasma flow with these diuretics.

Hypotensive Action: The benzothiadiazine diuretics reduce high but not normal blood pressures and potentiate the antihypertensive action of the rauwolfia and veratrum alkaloids, hydralazine, the ganglionic blocking agents (including the latest one, trimethidinium methosulfate) and the newest antihypertensive agents, guanethidine and bretylium tosylate. The dose of ganglionic blocking agents should be reduced by half when a "thiazide" saluretic is added to the regimen. The effective dose of these agents in patients who have had a sympathectomy may be as little as one-tenth the usual dose.

Side Effects and Electrolyte Disturbances: The side effects of thiazide diuretics are usually minimal but include nausea, anorexia, skin rashes and other allergic manifestations. More important is the possibility of electrolyte abnormalities such as hyponatremia, hypochloremia, hyperuricemia, metabolic alkalosis and hypokalemia. Except for the latter, these abnormalities are usually transient and asymptomatic. Administration of chlorothiazide has apparently precipitated clinical gout although the elevated serum uric acid produced usually causes no symptoms. No clinical cases of gout have been reported for the flumethiazide series; administration of flumethiazide and hydroflumethiazide produces only a small initial increase in serum uric acid which returns toward normal on continued therapy. Patients who have had gout while receiving chlorothiazide have continued on flumethiazide without recurrence

TABLE I
Commercially Available Benzothiadiazine (Thiazide) Diuretics

Generic Name	Trade Name(s)	Manufacturer	Range of Usual Daily Dose (mg.)
Chlorothiazide	Diuril®	Merck	250–2,000
Flumethiazide	Ademol®	Squibb	250–2,000
Hydrochlorothiazide	Hydro Diuril	Merck	25–200
	Esidrix®	Ciba	25–200
	Oretic	Abbott	25–200
Hydroflumethiazide	Di-Ademil®	Squibb	25–200
	Saluron	Bristol	25–200
Benzydroflumethiazide	Naturetin	Squibb	2.5–20

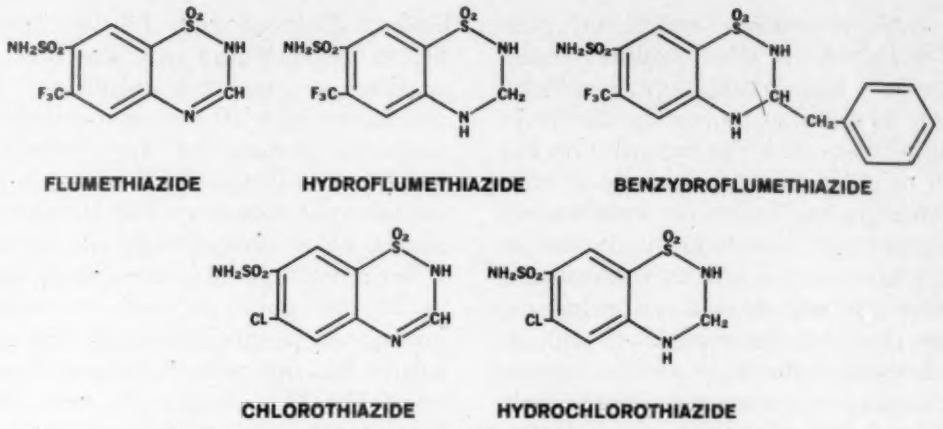


FIG 1. Structural formulas of benzothiadiazine compounds.

of symptoms. Thrombocytopenic purpura has occurred in patients receiving chlorothiazide but not in patients receiving other thiazides. This may be a matter of insufficient clinical experience with the newer drugs rather than a real difference. Allergic reactions to administration of chlorothiazide or hydrochlorothiazide have disappeared when the patients were transferred to flumethiazide or hydroflumethiazide with continuation of equivalent diuretic or antihypertensive actions. Hyperglycemia and glycosuria may also develop.

Hypokalemia: The most serious side effect of these diuretics is hypokalemia which occurs in as many as 40 per cent of patients receiving chlorothiazide or hydrochlorothiazide without supplementary potassium. Although clinical signs are not noted in many patients with a chemical hypokalemia, lassitude, lethargy, muscle weakness and cardiac arrhythmias, frequently associated with digitalis intoxication, do occur regularly. Complete muscular paralysis accompanied by hypokalemia has been reported in a patient receiving chlorothiazide. For this reason patients receiving these drugs should supplement their normal dietary intake with 1 to 6 gm. daily of potassium chloride or citrate. However, hypokalemia due to administration of chlorothiazide or hydrochlorothiazide is not always corrected by the usual doses of supplementary potassium salts.

Comparison of Various Thiazide Derivatives: Replacement of the chlorine group of chlorothiazide and hydrochlorothiazide with the trifluoromethyl group of flumethiazide and hydroflumethiazide appears to result in decreased potassium bicarbonate excretion at doses producing equivalent losses of sodium chloride and water. Thus, in one study ten patients under controlled metabolic conditions were each given alternately 1 gm. of flumethiazide and 1 gm. of chlorothiazide with a five- to seven-day interval between to permit a return to control status. No significant differences were observed between the two drugs in their effect on the amounts of sodium, chloride and urine excreted in the twenty-four hours after the drug was given. However, the average excretion of potassium in the twenty-four hours after administration of flumethiazide was 9 mEq. as compared with an excretion of 17 mEq. for the same period after 1 gm. of chlorothiazide was given. The corresponding values for bicarbonate were 6 mEq. with flumethiazide and 15 mEq. with chlorothiazide. Administration of flumethiazide caused an increase in pH of only 0.5 over the control level (pH 5.2 increased to 5.7) whereas administration of chlorothiazide caused an increase of 2 (pH 5.2 increased to pH 7.2). Animal and human pharmacology and clinical experience indicate that at doses producing the same loss of sodium chloride and water, benzydroflumethiazide produces less potassium bicarbonate loss than the other diuretics of this type.

The addition of two hydrogen atoms to the chlorothiazide or flumethiazide molecule to form the corresponding "hydro" derivative increases the potency somewhat more than tenfold. Thus, a 50 mg. tablet of hydrochlorothiazide appears to be somewhat more effective as a saluretic, diuretic and antihypertensive agent than a 500 mg. tablet of chlorothiazide. However, these two diuretics, and flumethiazide and probably hydroflumethiazide as well, have the same natriuretic effect when compared at their optimal doses or the same fraction thereof. They are also probably equally as effective di-

uretics or antihypertensive agents in most patients when given at their optimal doses. However, there is apparently some specificity in the reaction of different patients to the drugs in this group. Those few patients who do not respond well to chlorothiazide initially or after months of therapy may respond satisfactorily to hydrochlorothiazide or one of the flumethiazide series. Chloruresis is less than natriuresis with chlorothiazide and flumethiazide but exceeds sodium excretion following hydrochlorothiazide or hydroflumethiazide administration. Potassium excretion does not rise proportionately with sodium and chloride excretion as dose is increased, particularly with flumethiazide and hydroflumethiazide.

Clinical Studies in Heart Failure and Hypertension: Recent clinical studies on benzydroflumethiazide have been made by Dr. Ralph V. Ford, Houston, Texas, in the treatment of edema, and by Dr. Burton M. Cohen, Elizabeth, New Jersey, in the treatment of hypertension. They studied separate groups of five or more patients under standardized metabolic ward conditions and found that 5 mg. of benzydroflumethiazide induced much greater increases in water, sodium and chloride excretion, but smaller increases in potassium and bicarbonate excretion than did 1 gm. of chlorothiazide. Five mg. of benzydroflumethiazide also induced greater increases in water loss and smaller increases in potassium and bicarbonate excretion than did 50 mg. of hydrochlorothiazide, but about the same increase in the excretion of sodium and chloride. Increases in urinary pH averaged 2 for this dose of chlorothiazide, 0.8 for the hydrochlorothiazide, and 0.2 for the benzydroflumethiazide. The average weight loss in twenty-four hours for similar separate groups of ten cardiac patients each following administration of 1,000 mg. of chlorothiazide was 0.7 lb., after 50 mg. hydrochlorothiazide 0.9 lb. and after 5 mg. benzydroflumethiazide 1.4 lb. Treatment of twenty patients having edema due to cardiac, cirrhotic, or nephrotic conditions, steroids, or pregnancy with 10 mg. benzydroflumethiazide daily for twenty-one days resulted in good weight loss without significant change in serum sodium, potassium, carbon dioxide combining power, blood urea nitrogen or hematocrit.

Benzydroflumethiazide in daily doses of 12.5 to 20 mg. daily reduced the average blood pressure of twenty previously untreated hypertensive patients with Smithwick grades 2 to 4 from 184/115 to 156/95 mm. Hg. When benzydroflumethiazide was substituted for chlorothiazide in one-hundredth the dose, the average blood pressure of a group of five patients decreased from 164/104 to 156/95 mm. Hg. Substitution of one-tenth the dose of benzydroflumethiazide for hydrochlorothiazide or hydroflumethiazide resulted in further decreases in blood pressure averaging 170/111 to 159/96 mm. Hg and 152/99 to 145/92 mm. Hg, respectively. Of the thirty-nine patients in these groups receiving benzydroflumethiazide as the sole treatment for hypertension, twenty-eight remained entirely free of untoward effects throughout the period of treatment. Among the remaining patients, untoward occurrences had the following incidence: cramps in the leg, four; abdominal cramps, two; diarrhea, three; nausea, three; paresthesia, one; pruritus, two; and skin rash, one.

The data summarized in the previous two paragraphs illustrate the results obtained with benzydroflumethiazide in more than 1,000 patients with edema and hypertension in Europe and America. This new diuretic is the most potent available. It appears to be safer, partly because of its decreased effect on potassium excretion, and perhaps, because it is also more effective than other diuretics of this type. Further studies are awaited with interest.

Book Reviews

Reminiscences and Adventures in Circulation Research, by Carl J. Wiggers. Grune & Stratton, New York, 1958, pp. 404, $9.75.

In this potpourri of sound advice, sage observations and earthy humor Dr. Wiggers plays the role of the scientist's Dr. Spock. He endeavors to recapture some of the incidents and accidents that have molded his career, to recall some adventures in cardiovascular research and to record impressions of people, places, institutions and organizations that have advanced medical science during the past half century.

Book I relates the environmental and educational influences which started this distinguished physiologist on a fruitful scientific career in research and teaching. It shows how the child is father of the man and how important early training is in guiding children into science. He encourages parents to rear children along the paths of inquisitiveness, honesty, diligence and thrift—all important traits of the true scientist.

He believes the basic aim of medical education is to drill students in the art of logical thinking and analysis. From his experience he advises that the maturation of the investigator requires capacity to keep up in one's own field by writing, by acquaintanceship with persons who write, by regular reading habits, by efficient use of time, and by developing the ability to evaluate articles and to judge the validity of results. To Dr. Wiggers writing is a part of the profession of medicine in which the ability to express one's self and to communicate clearly is imperative. A knowledge of foreign languages is also important to the scientist. Of German descent, Dr. Wiggers learned German early in life and later acquired proficiency in French and Spanish through self-study.

Book II summarizes the diversified cardiovascular researches of the author and his associates for the past fifty years. This résumé provides an excellent introduction and background to the development of modern cardiology and physiology. Comments about research methods, equipment and the interpretation of data make this a valuable section to read. Personal opinions of Dr. Wiggers and anecdotes about the numerous scientists he trained or with whom he worked and fought season these observations.

Although Dr. Wiggers calls this book a monograph in the preface, it is actually an attempt at autobiography which, written in the sunset of life, provides the opportunity of reviewing his life and accomplishments for the benefit of society and the evaluation of posterity. Dr. Wiggers presents an excellent objective and analytic view of his life; but, as he writes, "The sketches of former associates, pupils and acquaintances among men of science are in some cases brief biographic notes: more often they are intended to portray personalities and their impact on research. If there are misjudgments of personalities, this reflects solely on the author's analytic capacity, for, unfortunately, the human brain with its sensory receptors, like an inadequate pulse pressure recorder, tends to magnify some components, attenuate others, and introduce artifacts that may make the characterizations unreal."

Missing, or perhaps too greatly damped, in this volume are the human foibles, the emotional frailties, the family relationships and the moral evaluations so essential for the complete appreciation of a person's life and times. The most significant autobiographies, like those of John Stuart Mill and Benjamin Franklin, record with frankness and honesty the movements of inner life and paint the intellectual and emotional crises present in all lives, even those of scientists. As John Stuart Mill has observed, "The habit of analysis has a tendency to wear away the feelings: as indeed it has, when no other mental habit is cultivated and the analysing spirit remains without its natural complements and correctives." The character of a truly great teacher and scientist must undoubtedly have a human and emotional component which must be recognized, captured and reproduced with feeling in a good autobiography. Since no scientist lives by reason alone without being influenced by feeling no matter how carefully he tries, the reviewer would like to see this concealed aspect of Dr. Wigger's life explored. Perhaps Dr. Wiggers will do it himself. If not, then a competent biographer should tackle the task.

The reviewer enjoyed this book by a man whose long and distinguished career in academic science entitles him to the well earned respect of mankind. Its style, although pedestrian and heavy at times, is lucid. If it were studied and followed by other scientific writers, it would ease the reading burden of editors, reviewers and others trying to keep up with the medical literature.

This book is recommended to parents, and especially to the wives of doctors and scientists upon whom falls the burden of rearing and training children. It should interest the young person considering an ascetic career in science and the cardiologist or physiologist seeking background information, much of which remains valid today, on cardiovascular progress in the last fifty years by the man responsible for much of it. RAYMOND HARRIS, M.D.

Malformaciones Cardiovasculares Congenitales, by Jorge Espino Vela. Edicion del Instituto Nacional de Cardiologia, Mexico City, 1959, pp. 389.

The main value of this monograph is that it is based on experiences accumulated on 2,500 patients with congenital cardiac malformations who were studied at the National Institute of Cardiology of Mexico. It presents in a very simple way the diagnostic problems as they were handled at this Institute.

There are interesting chapters, such as the one dealing with Lutembacher's disease. Thirteen patients, eight of them with postmortem confirmation, are described. The postmortem examination disclosed double mitral disease (stenosis and insufficiency), involvement of the tricuspid valve and sometimes involvement of the aortic valve. The clinical picture was dominated by the rheumatic valvular disease. It is concluded that the diagnosis should be suspected when there is cyanosis and the auscultatory signs of mitral valve disease are atypical.

The main criticism of the monograph is that it does not present the modern concepts of classification of each particular malformation. The author does not discuss the anatomic and hemodynamic concepts of Eisenmenger's complex and reaction, the transformation of ventricular septal defects and the interesting problems of the outflow tract of the right and left ventricle that lead to idiopathic obstructions. Also the highly technical laboratory diagnostic procedures that are so valuable are not bridged with the physical signs of the patient in the way that has been so successfully carried out by Wood and Leatham. The modern technics such as oximetry, dye dilution curves, foreign gases, as well as selective angiocardiography and retrograde aortography are not used or discussed. EPHRAIM DONOSO, M.D.

Teoria and Practica de la Electrocardiografia, by Enrique Cabrera. La Prensa Medica Mexicana Mexico City, 1958, pp. 222.

This is a simple and practical presentation of electrocardiography and vectorcardiography. The chapters on ventricular gradient, atrial and ventricular overloadings, and intraventricular conduction abnormalities are discussed in a very original, logical and personal way and show clearly that the student has superseded his teacher. Cabrera's ideas and concepts are presented throughout this monograph which is dedicated to the Spanish speaking cardiologists, but they deserve to be translated into English. EPHRAIM DONOSO, M.D.

RECEIVED FOR REVIEW

All books received will be acknowledged in this column. Insofar as possible, as space permits, books of special interest will receive more extensive reviews.

Pathology of the Heart, second edition, edited by S. E. Gould. Charles C Thomas, Springfield, Ill., 1959, pp. 1138, $32.50.

Les Hémiplégies Vasculaires, by Jean Minvielle and Boris Vlahovitch. Masson et Cie, Paris, 1959, pp. 227, 3,800 fr.

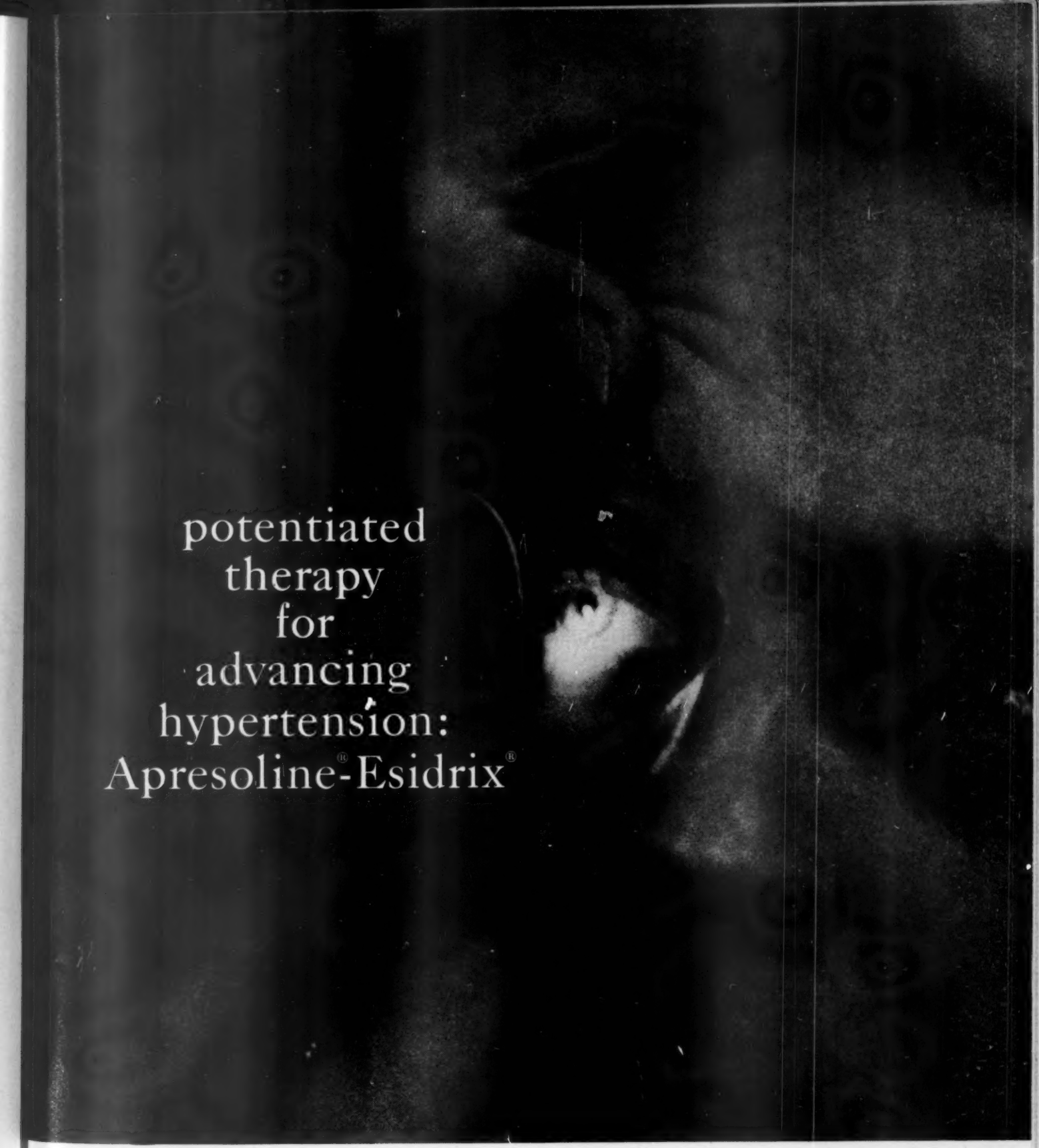
L'Électrocardiogramme Dysmetabolique. Perturbations Ioniques et Électrocardiogramme, by A. Larcan and C. Huriet. Masson et Cie, Paris, 1959, pp. 221, 2,500 fr.

Électrocardiographie Clinique. Theorie et Pratique, by Enrique Cabrera. Masson et Cie, Paris, 1959, pp. 258.

Grundriss und Atlas der Elektrokardiographie, by Rudolf Zuckermann. Georg Thieme Verlag, Leipzig, 1959, pp. 660, DM 72.15.

Diagnosis and Treatment of Tumors of the Chest, by David M. Spain. Grune & Stratton, New York, 1960, pp. 371, $14.75.

Microchemical Methods for Blood Analysis, by Wendell T. Caraway. Charles C Thomas, Springfield, Ill., 1960, pp. 109, $5.25.



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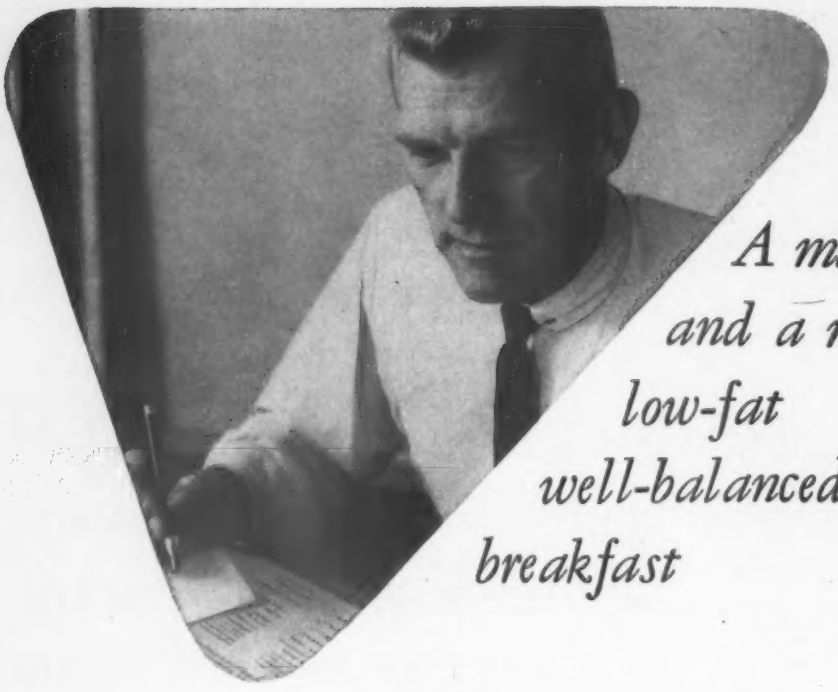

A man of 45 and a moderate low-fat well-balanced breakfast

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recommended dietary allowances* and the nutritional contribution of a basic cereal and milk moderate low-fat breakfast

Menu: Orange Juice—4 oz.;
Cereal, dry weight—1 oz.;
Whole Milk—4 oz.; Sugar—1 teaspoon;
Toast (white, enriched)—2 slices;
Butter—5 gm. (about 1 teaspoon);
Nonfat Milk—8 oz.

Nutrients	Calories	Protein	Calcium	Iron	Vitamin A	Thiamine	Riboflavin	Niacin equiv.	Ascorbic Acid
Totals supplied by Basic Breakfast	503	20.9 gm.	0.532 gm.	2.7 mg.	588 I.U.	0.46 mg.	0.80 mg.	7.36 mg.	65.5 mg.
Recommended Dietary Allowances—Men, 45 Years (70 kg.—154 lb.)	3000	70 gm.	0.8 gm.	10 mg.	5000 I.U.	1.5 mg.	1.8 mg.	20 mg.	75 mg.
Percentage Contributed by Basic Breakfast	16.8%	29.8%	66.5%	27.0%	11.8%	30.7%	44.4%	36.8%	87.3%

Cereal Institute, Inc.: Breakfast Source Book. Chicago: Cereal Institute, Inc., 1959.

Food & Nutrition Bd.: Recommended Dietary Allowances, Revised 1958. Natl. Acad. Sci.—Natl. Research Council Publication 589, 1958.

Watt, B. K., and Merrill, A. L.: Composition of Foods—Raw, Processed, Prepared. U.S.D.A. Agriculture Handbook No. 8, 1950.

**The allowance levels are intended to cover individual variations among most normal persons as they live in the United States under usual environmental stresses. Calorie allowances apply to individuals usually engaged in moderate physical activity. For office workers or others in sedentary occupations they are excessive. Adjustments must be made for variations in body size, age, physical activity, and environmental temperature.*

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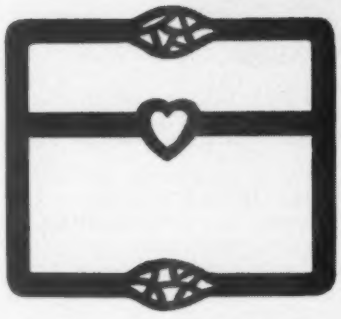

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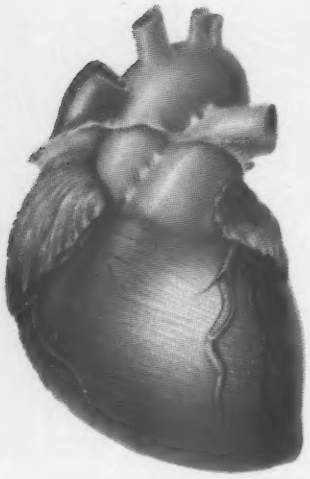

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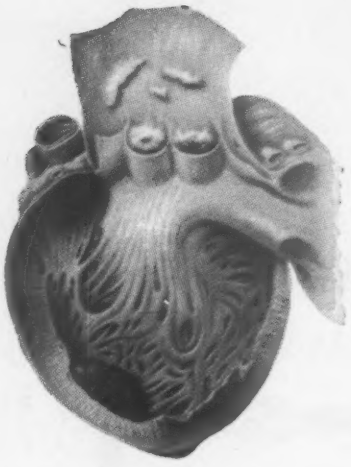

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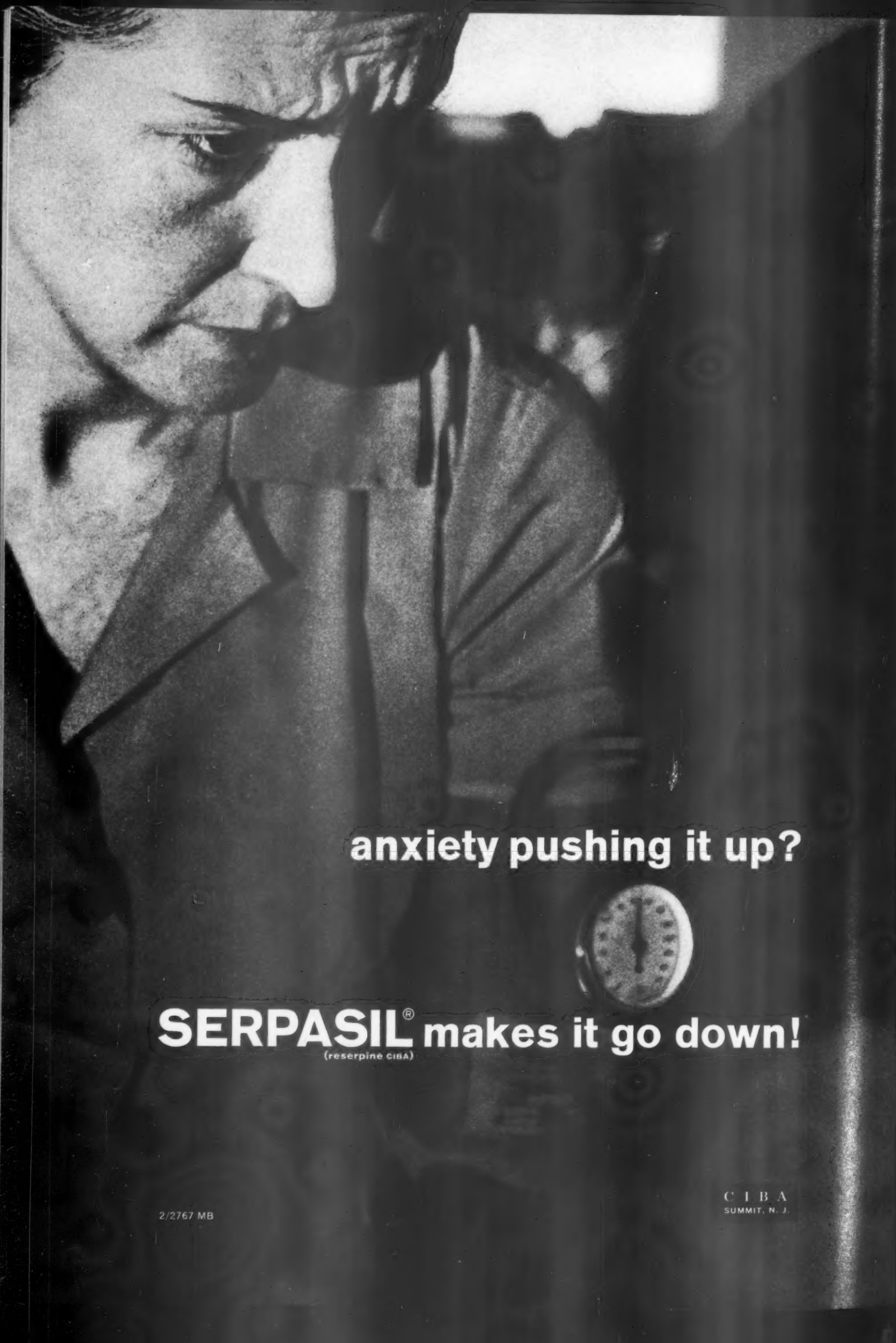
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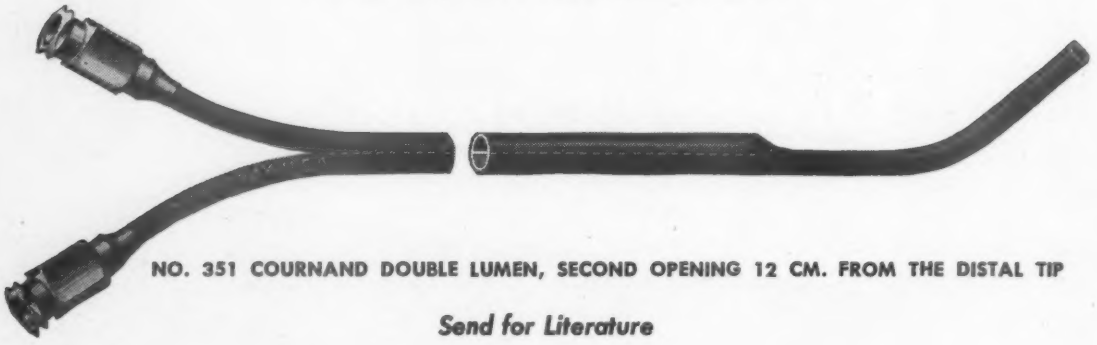

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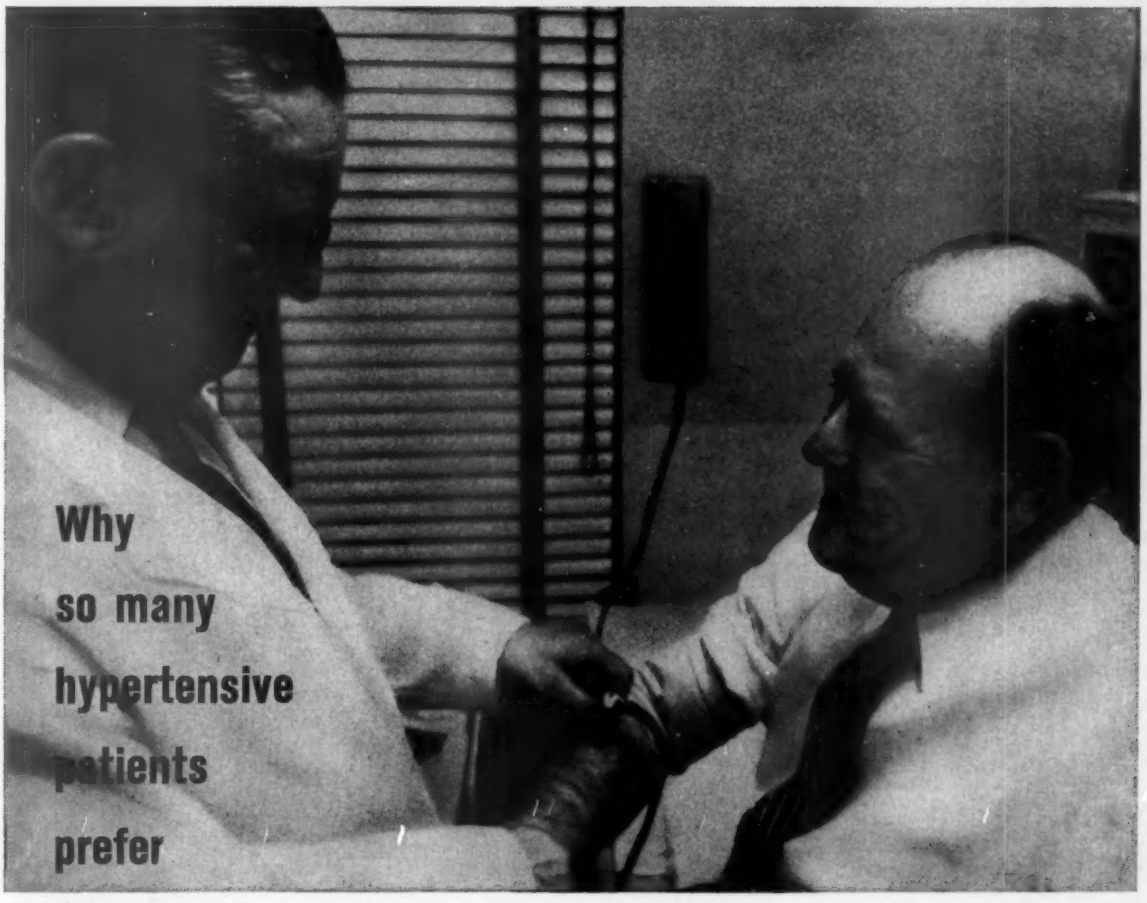

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*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.

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First drug to add in hypertensive patients already on medication

SUPPLIED: Singoserp *Tablets*, 1 mg. (white, scored); bottles of 100. Samples available on request. Write to CIBA, Box 277, Summit, N. J.

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brand of ethyl biscoumacetate

when medium rate of action with more sustained effect is desired

Sintrom®
brand of acenocoumarol

With Tromexan, a therapeutic hypoprothrombinemia is achieved in 18 to 24 hours. In case of accidental overdosage, simple omission of the next scheduled dose assures rapid return of prothrombin time to safe limits.

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to prevent or treat thromboembolic disease

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reduces the impact of emotional stress—
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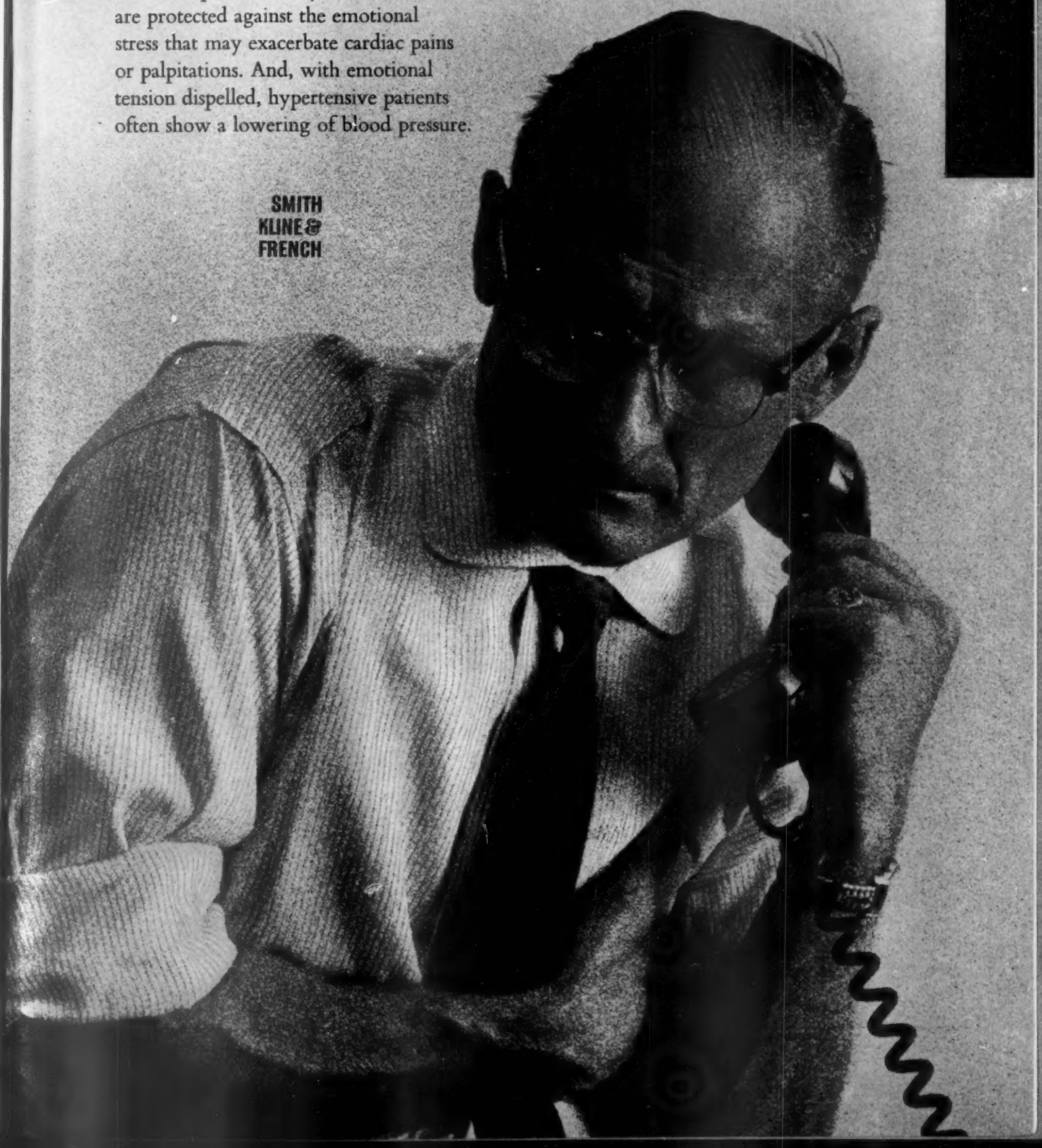

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"I favor ATARAX [as the tranquilizer for the anxious cardiac] ... because there is an absence of side effects with this drug, and also because in cardiacs who are troubled with ectopic beats, ATARAX has a quinidine-like action."[2]

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Dosage: Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. When indicated, this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. ATARAX). For convenience, write "CARTRAX 10" or "CARTRAX 20." **Supplied:** In bottles of 100. Prescription only.

References: 1. Russek, H. I.: Postgrad. Med. 19:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1958.

*brand of hydroxyzine

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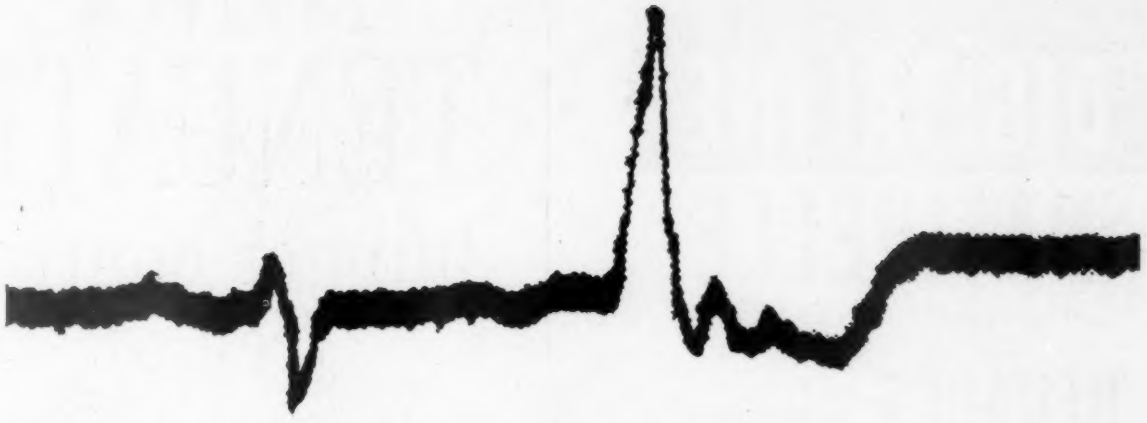

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References: 1. Zapata-Diaz, J., et al.: Am. Heart J. 43:854, 1952. 2. Modell, W.: In Drugs of Choice, C.V. Mosby Co., St. Louis, 1958, p. 454.
3. Kayden, H. J., et al.: Mod. Concepts Cardiovasc. Dis. 20:100. 1951. 4. Miller, H., et al.: J.A.M.A. 146:1004, 1951.

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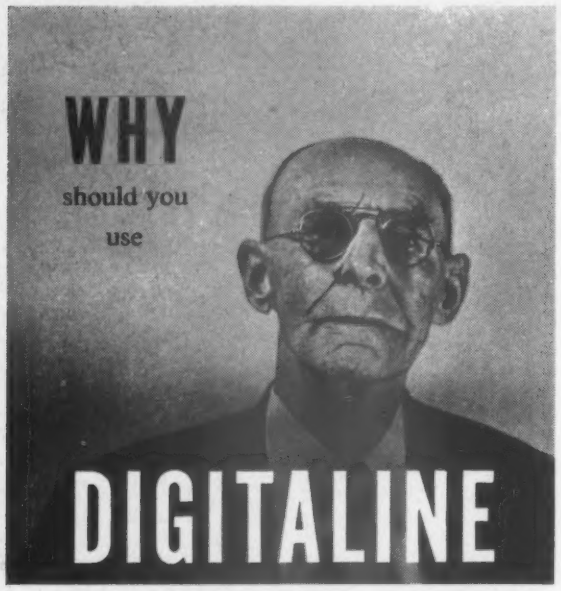

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for the cardiac/
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hunger control free of pressor effects

New Tenuate produces a pure anorexic effect, free of CNS stimulation.[1] EKG studies[2] prove Tenuate does not affect heart rate, blood pressure, pulse or respiration.

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Dosage: *One 25 mg. tablet one hour before meals. To control nighttime hunger, an additional Tenuate tablet in mid-evening will not induce insomnia.*

hunger control for any obese patient

1. Spielman, A.D.: Mich. Acad. Gen. Prac. Symposium, Detroit, 1959.
2. Alfaro, R. D. and Gracanin, V.: *to be published.*

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of cardiac patients

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Clarin* can do this for your postcoronary patients

WITHOUT CLARIN, turbid blood serum five hours after a fat meal: This unretouched dark-field photomicrograph (2500X) shows potentially hazardous fat concentrations circulating in the blood stream of a patient after a standard fat meal.

WITH CLARIN, clear blood serum five hours after a fat meal: After eating a standard fat meal as at left, the same patient has taken one sublingual Clarin tablet. Note marked clearing effect and reduction in massive fat concentrations in this unretouched photomicrograph (2500X).

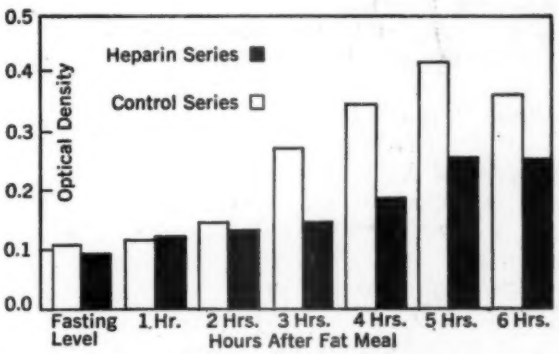
CLARIN is sublingual heparin potassium. One mint-flavored tablet taken after each meal effectively "causes a marked clarification of postprandial lipemic serum."[1] Clarin facilitates the normal physiologic breakdown of fats, with no effects on the blood-clotting mechanism.[1] It therefore provides important benefits for your postcoronary patients.

Indication: For the management of hyperlipemia associated with atherosclerosis.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

1. Fuller, H. L.: Angiology *9*:311 (Oct.) 1958.
2. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959.

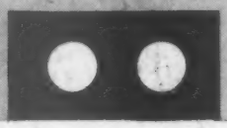


Average serum optical density in 36 patients after fat meal with and without sublingual heparin.[2]

*Registered trade mark. Patent applied for.

Thos. Leeming & Co., Inc. New York 17, N. Y.

NOV 17 1962
5 1960
SEP 28 1962

Just two tablets  *at bedtime*

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alseroxylon, 2 mg.

...does more than lower blood pressure!

Seven years of experience show
that RAUWILOID also affords

Safety based on negligible incidence of side actions

Freedom from concern over sudden hypotensive episodes or unwanted biochemical alterations

Practicality..simplicity of dosage ..applicable to a wide range of patients

When more potent drugs are needed, prescribe one of the *convenient single-tablet combinations*

Rauwiloid® + Veriloid®
alseroxylon 1 mg. and alkavervir 3 mg.

or

Rauwiloid® + Hexamethonium
alseroxylon 1 mg. and hexamethonium chloride dihydrate 250 mg.

Many patients with severe hypertension can be maintained on Rauwiloid alone after desired blood pressure levels are reached with combination medication.

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Northridge, California